Asymptomatic carotid artery stenosis

- Population Based Screening -

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- Population Based Screening -

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- Screening van de algemene bevolking -
(met een samenvatting in het Nederlands)

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Manuscripts based on the studies presented in this thesis

Chapter 1
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Chapter 2
de Weerd M., Greving JP., de Jong AW., Buskens E., Bots ML.:Prevalence of asymptomatic carotid artery stenosis according to age and sex: systematic review and metaregression analysis. *Stroke 2009;40;1105-13*

Chapter 3
de Weerd M., Greving JP., Hedblad B., Lorenz MW., Mathiesen EB., O'Leary DH., Rosvall M., Sitzer M., Buskens E., Bots ML.: Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis. *Accepted for publication in Stroke*

Chapter 4
de Weerd M., Greving JP., Algra A., van der Graaf Y., Kappelle LJ., Bots ML., Buskens E.: Cost-effectiveness of one-time screening for asymptomatic carotid arterial stenosis in the general population. *Submitted*

Chapter 5
de Weerd M., Greving JP., Algra A., van der Graaf Y., Kappelle LJ., Bots ML., Buskens E.: Cost-effectiveness of one-time screening for asymptomatic carotid arterial stenosis followed by endarterectomy and/or cardiovascular risk factor management. *Submitted*

Chapter 6
de Weerd M., Greving JP., Hedblad B., Lorenz MW., Mathiesen EB., O'Leary DH., Rosvall M., Sitzer M., Buskens E., Bots ML.: Prediction of asymptomatic carotid artery stenosis in the general population. *Submitted*

Contents

Chapter 1

General Introduction

Cardiovascular disease is one of the leading causes of disability and death worldwide and imposes a substantial burden on healthcare budgets[1]. Of cardiovascular diseases stroke is the leading cause of hospitalization and death in both men and women in nearly all European countries and the third major cause of death in the United states[2-4]. Carotid artery stenosis is an important risk factor for stroke. Studies have reported an annual risk of stroke of approximately 2% to 6% for patients with severe asymptomatic carotid artery stenosis. Severe asymptomatic carotid artery stenosis generally means atherosclerotic narrowing of the carotid artery exceeding 60-70% of the lumen diameter [5]. This deformation at least in Western communities, becomes increasingly prevalent with advancing age[5].

Secondary prevention

Patients with severe carotid artery narrowing are at increased risk of suffering a disabling or fatal ischaemic stroke in the carotid territory of the brain. The hazard is greater if the stenosis is already symptomatic, i.e., if the individual recently suffered some relevant neurological symptom, such as stroke or TIA in the parts of the brain supplied by the carotid arteries[6]. For these patients effective preventive treatment is available. In case of over 69% stenosis, carotid endarterectomy may be offered[7;8]. Carotid endarterectomy (CEA) is one of the most common procedures in vascular surgery effectively reducing the risk of stroke in patients with symptomatic carotid artery stenosis[7;8]. In symptomatic patients with less severe stenosis (50-70%) cardiovascular pharmacotherapy has been proven beneficial[7;8]. However, prior to becoming symptomatic the vascular disease has progressed in thus far asymptomatic patients. Then, the disorder becomes manifest and a TIA or actual stroke occurs. As mentioned above secondary prevention may limit some of the burden of recurrent disease. However, for a considerable number of patients this may come too late. They are immediately faced with the consequences of severe stroke and may, even with acute treatment, die or become dependent for daily activities. Effective primary prevention, prior to becoming symptomatic might prevent part of these devastating outcomes.

Primary prevention

Recently evidence had become available[6;9] showing that also for asymptomatic patients with severe stenosis an surgery may yield overall beneficial effects [6;9;10]. Despite differences in primary outcome measures, there was an absolute overall reduction of approximately 1% in average annual stroke risk among asymptomatic patients who underwent CEA[11]. In some countries CEA for asymptomatic carotid artery stenosis is supported by best practice guidelines[12-14].

Alternative means of primary prevention such as pharmaceutical interventions have also been conceived. Clinical trials have shown the beneficial effects of cardiovascular risk factor management, using hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) and blood pressure lowering medication (for example ACE-inhibitors, diuretics, beta-blockers, calcium antagonists, angiotensin blockers) in reducing mortality and vascular morbidity in patients with symptomatic cardiovascular disease[15]. In patients without symptomatic cardiovascular disease but with cardiovascular risk factors, cardiovascular risk factor management was associated with significantly improved survival and large reductions in the risk of major vascular events[16].
Thus, the question arises whether we should actively trace and treat individuals with asymptomatic carotid artery stenosis. This question pertains to several potential
(sub-)groups of the population, and also has bearing on the age at which to start screening.

Screening

Presently, most neurologists, general practitioners and others involved in the care for potential candidates for screening and subsequent intervention tend to be conservative. Indeed, current guidelines suggest being cautious with invasive surgical therapies in asymptomatic patients[17-19]. Others take a more offensive position and suggest screening at least for high risk groups[20].

Prevalence of asymptomatic carotid artery stenosis

For estimation of the cost-effectiveness of screening for asymptomatic carotid artery stenosis, good prevalence estimates of asymptomatic carotid stenosis are essential. Given that the frequency of carotid artery disease in the general population steadily increases with age, it is very relevant to provide precise accurate age- and sex-specific data on the prevalence of asymptomatic carotid stenosis in the general population,

The current studies on prevalence of ACAS are difficult to use since methods to assess carotid stenois were different, and a large number of studies were not population based but patient based, which may have biased prevalence rates upward. One study[12] used prevalence estimates of asymptomatic carotid artery stenosis, based on different definitions of carotid artery disease for the estimation of the cost-effectiveness. For instance some studies[21;22] use carotid intima-media thickness measurements (CIMT) while in other studies a percentage of stenosis was

reported. CIMT provides information different from degree of stenosis. Additionally, prevalence estimates used in this study were not general population based studies. Inclusion of many individuals with hypertension for instance introduces bias when making recommendations for the general population[23].

Balancing costs and effects
Immediate postoperative outcomes as well as long-term outcomes in non-selected populations and, importantly, non-selected surgical centres, continue to be debated. Clearly a surgical intervention that would half the 5-year risk of stroke appears interesting[6;9]. For instance, screening a high-risk population with peripheral arterial disease (PAD), with an estimated prevalence of asymptomatic carotid artery stenosis of 14% may appear promising[24]. However, as the life expectancy of patients with PAD is considerably reduced it is not at all clear whether a relevant (survival) benefit would actually ensue from a reduction in the risk of ischemic stroke that may only accumulate in the long run. Particularly because issues such as competing morbidity and mortality have not been taken into account in balancing costs and effects in previous studies on carotid stenosis screening, the proper management of people with asymptomatic carotid stenosis remains controversial[25].

In conclusion, carotid artery stenosis appears to remain a severe condition with prevalence increasing with age. The need for additional research taking into account long-term outcomes and the balance between costs and effects, rather than a seemingly premature advice on screening and subsequent invasive preventive therapies, is apparent. This formed the basis for the work described in this thesis.

Outline of this thesis
The main objective of this thesis was to find out whether screening for asymptomatic carotid artery stenosis in the general population is worthwhile. The studies in this thesis will show whether the prevalence of asymptomatic carotid artery stenosis indeed represents a relevant potential burden amenable to screening. This obviously also pertains to the subsequent treatment available, i.e., only with an effective and safe treatment available screening might be recommended.

The first part of this thesis focuses on the prevalence of asymptomatic carotid artery stenosis.
Chapter 2 describes the prevalence of asymptomatic carotid artery stenosis in the general population, giving an overview of the literature using meta-regression

analysis models. **Chapter 3** presents the prevalence of asymptomatic carotid artery stenosis in the general population using the individual participant data from four large population-based cohort studies.
The second part of this thesis focuses on the cost-effectiveness of non-invasive screening for asymptomatic carotid artery stenosis in the general population. **Chapter 4** evaluates the cost-effectiveness of screening, followed by endarterectomy after finding severe (> 70%) stenosis.
Chapter 5 addresses the cost-effectiveness of screening followed by endarterectomy after finding severe stenosis and cardiovascular risk factor management after finding moderate (> 50%) stenosis.
The last part of this thesis focuses on the identification of persons with a high probability of having moderate or severe stenosis based on findings from the earlier chapters. **Chapter 6** provides prediction models for moderate or severe stenosis in the general population. Finally, in **chapter 7** the main findings and conclusions reported in this thesis are discussed and put into a general perspective for further improvement.

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Chapter 2

Prevalence of asymptomatic carotid artery stenosis according to age and gender: a systematic review and meta-regression analysis

Abstract

Background and Purpose
In the discussion on the value of population-wide screening for asymptomatic carotid artery stenosis (ACAS) reliable prevalence estimates are crucial. We set out to provide reliable age- and gender-specific prevalence estimates of ACAS through a systematic literature review and meta-regression analysis.

Methods
We searched PubMed and EmBase until December 2007 for studies that reported the prevalence of ACAS in a population free of symptomatic carotid artery disease. Data were extracted using a standardized form on participants' characteristics, assessment method, study quality and prevalence estimates for moderate (≥50% stenosis) and severe ACAS (≥70% stenosis). Meta-regression was used to investigate sources of heterogeneity.

Results
Forty studies fulfilled the inclusion criteria. There was considerable variation among studies with respect to demographics, methods of grading stenosis, and stenosis cut-off point used. The pooled prevalence of moderate stenosis was 4.2% [95% confidence interval (CI) 3.1-5.7%]. Prevalence of moderate stenosis among people aged <70 years was 4.8% (95%CI 3.1-7.3%) in men and 2.2% (0.9-4.9%) in women. Among those ≥70 years, prevalence increased to 12.5% (95%CI 7.4-20.3%) in men and 6.9% (95%CI 4.0-11.5%) in women. Meta-regression showed that both age and gender significantly affected the prevalence of moderate stenosis. No contribution of study size, publication year, geographic region, assessment method, and study quality was found. The pooled prevalence of severe stenosis was 1.7% (95%CI 0.7-3.9%).

Conclusions
Prevalence of moderate stenosis increases with age in both men and women, but men at all ages have the highest prevalence estimates. The number of studies that allowed meaningful data synthesis of severe stenosis was limited.

Introduction

Stroke is the leading cause of death and hospitalization in both men and women in nearly all European countries and the third major cause of death in the United States.[1,2] Carotid artery stenosis is one of the risk factors for stroke.[3,4] Studies have reported an annual risk of stroke of approximately 2-5% for patients with severe asymptomatic carotid stenosis.[4-7]
Carotid endarterectomy (CEA) is one of the most common vascular surgery procedures, and it reduces the risk of stroke in patients with symptomatic carotid stenosis.[8,9] However, despite the publication of several randomized controlled trials in asymptomatic patients[10,11], the role of CEA and non-invasive screening is still debated.[12-14] In part because accurate estimates of prevalence of carotid stenosis in different risk groups are missing. This precludes planning of effective screening and treatment of populations at (high) risk of severe asymptomatic carotid stenosis, who might benefit from preventive surgery.
We set out to provide reliable age- and gender-specific prevalence estimates of asymptomatic carotid artery stenosis through a systematic literature review and a meta-analysis.

Methods

Search strategy
We performed a PubMed and EmBase search to retrieve all published articles reporting on the prevalence of asymptomatic carotid artery stenosis from 1966 until December 2007. The following keywords were used: carotid arter* diseas* [Title/Abstract] or carotid arter* stenos* [Title/Abstract] or carotid stenos* [Title/Abstract] or carotid arter* atheroscleros* [Title/Abstract] combined with prevalence [All fields] or frequency [Title/Abstract] or occurrence [Title/Abstract]. A cross-reference check was performed to ascertain additional articles.

Study eligibility
We reviewed the abstracts to identify studies that satisfied the following predefined inclusion criteria. First, studies must have evaluated a population free of symptomatic carotid artery disease. Conversely, studies on patients with clinically manifest vascular disease, or patients at high risk for vascular events were excluded. Studies with information on the prevalence of asymptomatic carotid stenosis in the control groups of a clinical trial resembling the general population were also included. Second, studies were required to have reported

sufficient detail to allow estimating the prevalence of stenosis. Thus, studies with measurements of carotid intima media thickness of plaques only were not included. We included cross-sectional and cohort study designs and articles in any language. Studies were included only once if there were multiple publications concerning the same study population.

Data extraction

Two investigators (MdW and AWFdJ) selected the studies to be included in the review, extracted the data independently, and cross checked them with disagreement resolved by discussion with a third reviewer (either JPG or MLB). The following data was extracted from each study: description of the population characteristics (publication year, type of population, country, number of included participants, age range, mean age, sex distribution), assessment method, method of measurement of carotid stenosis and carotid stenosis prevalence estimates. Data were extracted using standardized data extractions forms specifically created for this review and were subsequently entered into a database.

Where mean age was not stated, the population weighted mean or midpoint of the range was derived. Because in studies different cut-off points for stenosis were used we distinguished the following categories: moderate stenosis (≥50%) and severe stenosis (≥70%).

Quality assessment

Quality of all selected papers was assessed by one of the investigators (JPG) for the following attributes: (1) representation of the general population, (2) appropriate recruitment of the population, and (3) adequate response rate. In prevalence studies, the participants selected should be ideally be representative for the general population. Methods of achieving this may involve using population registries, inhabitants of a defined area, and people registered with a general practice. Participants attending health check-ups may be biased and only cover certain population groups. Recruitment was considered appropriate if recruitment of participants was random or consecutive rather than performed for convenience. A response rate of 50% or higher was considered adequate.

Data analysis

Prevalence estimates were, wherever possible, stratified by age and gender for each study. Outcome measures were pooled across studies using a random effects model which allows for heterogeneity of effects between studies.[15] To test our hypothesis concerning the effect of age and gender, a meta-regression model

was built with prevalence estimates of moderate stenosis as dependent variable. The covariates in this model were participants' mean age, percentage women, study size, publication year, geographic region, assessment method (Doppler vs. Duplex), and several quality indicators. Publication bias was examined visually with a funnel plot of study precision against effect size and statistically using Egger's test. A deficiency in the base of the funnel with asymmetry indicates the presence of possible publication bias from unpublished small studies. Statistical analyses were performed with SAS (version 9.1) and STATA (version 8.0).

Results

Figure 1 shows the consecutive steps that were followed to identify the appropriate studies. We identified 40 studies that fulfilled all inclusion criteria.[16-55] **Table 1** summarizes the characteristics of these studies. One of these publications was in Spanish[40], and the remaining 39 were in English. Three studies[26,45,55] examined over 5,000 individuals and contributed almost 50% of the total number of individuals. There was a considerable variation among studies with respect to demographics (age and gender distribution), methods of grading stenosis and the stenosis cut-off point used. Study quality assessment revealed deficiencies in many areas of methodology. Seven studies met all three quality criteria, ten studies met two criteria, seven met one criterion, and the remaining 15 studies met no quality criterion (**Table 1**).

Table 1. Overview of selected articles

Table 1. Overview of selected articles

First Author	Year	Population	No. of individuals	Age range (yr)	Mean age	♀ (%)	Excl. criteria	Stenosis criteria	Assessment method †	Classification of stenosis‡	No. of quality criteria (criteria§)	Prevalence moderate stenosis (≥50%)	Prevalence severe stenosis (≥70%)
Chan[16]	1983	One friend control was selected by each diabetic, Seattle, US	135	35-74	60	53	-	<50%, ≥50%	2	2	0	0.7	-
van Merode[17]	1985	Population sample Maastricht area, The Netherlands	93	50-69	ND*	0	IDDM, non-available lipid profiles	≤15%, 16-49%, 50-99%, 100%	1	2	3	5.4	-
Josse[18]	1987	Patients referred for ultrasonic examination of cervical arteries, Paris area, France	526	45-84	ND	58	Coronary and/or peripheral vascular diseases, risk factors for atherosclerosis	<15%, 15-50%, >50%	2	2	0	2.1	-
Ramsey[19]	1987	Volunteers church congregration, Illinois, US	102	50+	ND	56	-	<20%, 20-39%, 40-59%, 60-79%, 80-99%, 100%	2	2	0	-	1.0
Colgan[20]	1988	Volunteers at health fairs, Illinois, US	348	24-91	61	60	Cerebrovascular/ ocular symptoms	1-15%, 15-49%, 50-79%, ≥80%	2	2	0	3.7	0.9
Langsfeld[21]	1988	Volunteers at health fairs, Australia	153	40+	56	48	-	0-20%, 21-49%, ≥50%, and 100%	2	2	0	1.3	0.7
Salonen[22]	1988	Population sample Kuopi area, Finland	412	42-60	51	0	-	≤20%, >20%	2	1	1 (3)	-	-
Jungquist[23]	1991	Birth cohort of Malmö, Sweden	478	69	69	0	-	0-29%, 30-59%, ≥60%	1	2	2 (2,3)	-	3.1
Bots[24]	1992	Subsample of the Rotterdam study, The Netherlands	954	55+	ND	ND	-	0%, 1-15%, 16-49%, ≥50%	2	2	3	1.4	-
O'Leary[25]	1992	Population sample Framingham, US	1,189	66-93	ND	ND	ND	0%, 1-24%, 25-49%, 50-74%, 75-100%	2	2	2 (1,2)	7.6	2.4
O'Leary[26]	1992	Subcohort Cardiovascular Health Study, US	5,116	65+	ND	57	-	0%, 1-24%, 25-49%, 50-74%, 75-99%, 100%	2	2	3	6.2	1.6
Prati[27]	1992	Population sample Friuli-Venezia Giulia region, Italy	1,348	18-99	ND	53	Stroke survivors	<40%, ≥40%	2	2	3	-	-
Puija[28]	1992	Elderly from retirement homes, Seattle, US	239	65-94	ND	76	-	1-49%, 50-99%, 100%	2	2	1 (3)	4.6	-

Sutton-Tyrrell[29]	1993	Normotensive control subjects of SHEP, Pittsburgh US	187	60+	ND	59	Recent MI, stroke, heart failure, PAD, TIA,contraindication to study medication, systolic blood pressure <160 mm Hg.	<50%, ≥50%	2	2	0	7.0	-
Willeit [30]	1993	Population sample Bruneck, Italy	909	40-79	ND	49	CEA, TIA/CVA, missing lab data	<40%, 40-80%, >80%	2	1,2	3	-	1.8
Fabris[31]	1994	Population sample, Turin, Italy	457	18-97	55	49	-	<25%, 25-49%, 50-75%, 76-99%, 100%	2	1	3	3.9	0.9
Lindgren[32]	1994	Control subjects, Lund, Sweden	59	51-95	72	49	Stroke, TIA	<50%, 50-99%, 100%, and 80-99%	2	2	2 (1,2)	13.6	0
Pascazio[33]	1994	Normotensive controls matched for age, gender and cardiovascular risk factors, Trieste, Italy	71	64-91	73	35	Not free from coronary or cerebrovascular disease	<20%, 20-49%, ≥50%	2	2	0	7.0	-
Aronow[34]	1995	Elderly in a long-term health care facility, US	1,275	60-101	81	71	-	<40%, 40-80%, 81-99%, 100%	2	2	0	-	3.5
Auperin[35]	1996	Population sample Nantes, France	1,279	59-71	65	59	CVA	0-20%, 20-40%, and >60%	2	1	2 (1,2)	-	-
Harer[36]	1996	Population sample Moscow, Russia	529	36-84	58	35	ND	<50, 50-60%, 70-80%, 90-95%, 100%	1	2	0	4.2	2.8
Beks[37]	1997	Normal glucose tolerance group of the Hoorn Study, The Netherlands	287	50-74	63	48	Diabetes mellitus, impaired glucose tolerance	0-15%, 16-49%, ≥50%	2	2	2 (2,3)	2.8	-
Mannami[38]	1997	Population sample of Suita, Japan	1,445	50-79	63	53	-	<25%, 25-50%, >50%	2	1,2	1 (2)	4.4	-
Martyn[39]	1998	Birth cohort of Sheffield, UK	181	±70	68	33	-	0%, 1-30%, 31-50%, >50%	2	1	0	8.8	-
Rodriguez Saldana[40]	1998	Population sample CUPA project, Mexico City	198	60+	ND	72	ND	≤50%, >50%	2	?	?	6.1	-
Cheng[41]	1999	Healthy controls, Hong Kong, China	108	50+	62	61	-	0-29%, 30-69%, 70-99%, 100%	2	2	0	-	0
Meissner[42]	1999	Population sample Olmstad, US	567	45+	ND	ND	-	≤49%, 50-79%, 80-99%	2	2	2 (1,2)	8.1	0.4
Hillen[43]	2000	Healthy volunteers Berlin Ageing Study, Germany	225	70-100	80	41	Immobility, need of help or incontinence	≤50%, 51-75%, >75%	2	2	2 (2,3)	15.1	4.0
Mannami[44]	2000	Population sample, Ikawa,	249	50-69	60	0	-	<25%, 25-49%,	2	1,2	0	9.6	-

		Japan						≥50%					
Mathiesen[45]	2001	Population sample Tromsø study, Norway	6,420	25-84	ND	53	Persons from previous dietary trial	<35%, ≥35%	2	2	3	3.4	0.9
Su[46]	2001	Normotensive adults from the Chin-San Community Cardiovascular cohort, Taiwan	270	35+	64	58	-	<50%, ≥50%	2	2	2 (2,3)	1.5	-
Lernfelt[47]	2002	Birth cohort of Gothenburg, Sweden	142	78	78	50	People who lived in nursery homes	≤50%, 51-75%, >75%	2	2	1 (3)	22.5	4.9
Mineva[48]	2002	Population sample of the city of Stara Zogara, Bulgaria	500	50-79	ND	60	Clinical signs and symptoms of vascular diseases. Without cerebrovascular symptoms	0-49%, 50-79%, 80-99%	2	2	1 (2)	6.4	0.4
Luedemann[49]	2002	Population sample of northeast region of Germany	1,632	45-70	58	53	History of MI or stroke, complete data	≤50%, >50%	2	2	1 (3)	2.0	-
Wang[50]	2002	Offspring and spouses of the offspring Framingham Heart cohort, US	3,173	25-90	55	52	-	<25%, ≥25%,	2	2	2 (1,3)	-	-
Rosvall[51]	2002	Subcohort Malmö Diet and Cancer study, Sweden	4,208	46-68	ND	57	Technical problems duplex scan, missing lab data, homemakers	<15%, ≥15%	2	1	2 (1,2)	-	-
Alkaabi[52]	2003	Matched controls of the rheumatology out-patient clinics, Dundee, UK	40	36-73	55	50	History of inflammatory arthritis or vascular disease	<20%, 20-49%, 50-74%, ≥75%	2	1	0	0	0
Horner[53]	2005	Subsample from the Austrian Stroke Prevention Study (ASPS)	500	50-70	ND	ND	Not free from previous cerebrovascular attacks	<50%, 50-70%, and >90%	2	?	1 (1)	1.2	0.4
Takahashi[54]	2005	Matched controls of the HIMEDIC Imaging Center, Japan	605	54+	63	34	History of neurologic disorder, abnormal neurology manifestation	<25%, 25-49%, ≥50%	2	1	0	2.0	-
Hupp[55]	2007	Vascular screening program in Annapolis, Maryland	11,636	40-95	65	59	-	1-39%, 40-59%, ≥60%	2	2	0	-	-

* = Not documented
†1=Doppler, 2=Duplex
‡1=Lumen diameter reduction, 2=Peak Systolic Velocity Method
§ 1=Representation of the general population, 2=Appropriate recruitment of the population (random or consecutive), 3=Adequate response rate (≥50%)
Because the majority of the studies did not report the method of measurement (i.e. NASCET or ECST method) of stenosis, a column with this information was not added. When the method of measurement was reported, the NASCET method was used.

Figure 1. Results of search strategy

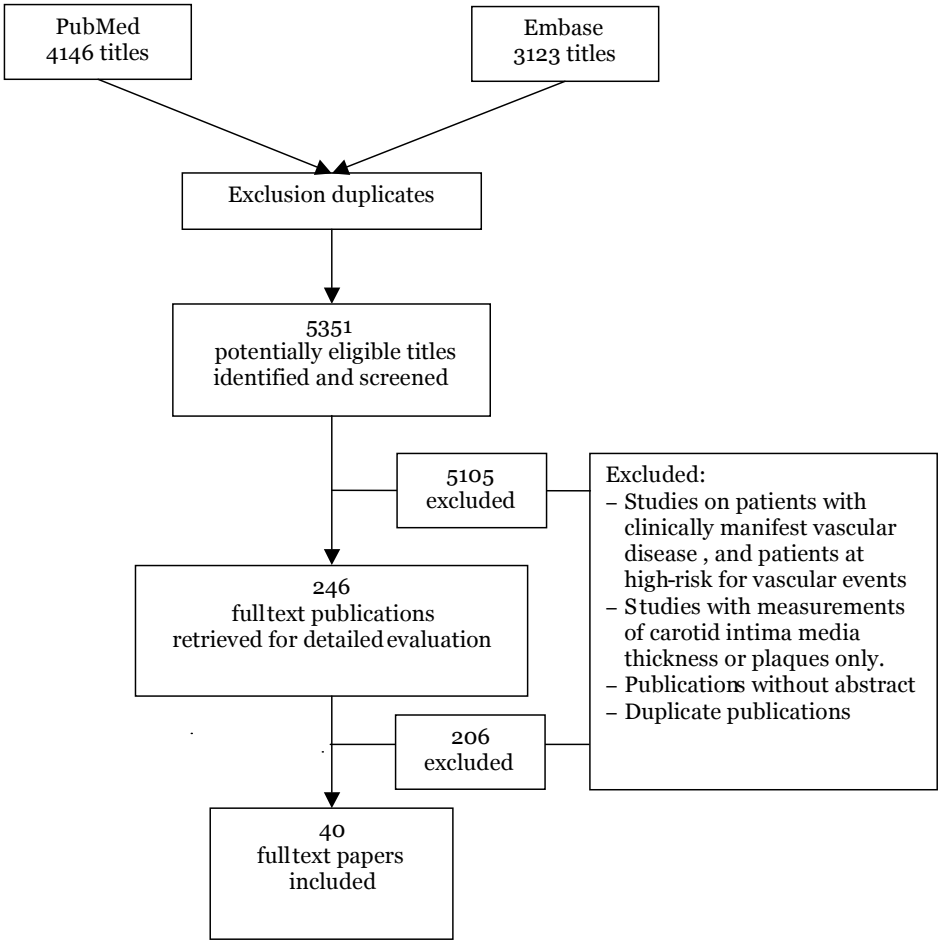

Figure 1. Results of search strategy

Moderate carotid artery stenosis

From 29 studies we obtained data on 22,636 individuals, including 959 persons with moderate carotid artery stenosis (≥50%).[16-18,20,21,24-26,28,29,31-33,36-40,42-49,52-54] Prevalence of moderate stenosis ranged from zero to 22.5%, with a pooled random effects prevalence estimate of 4.2% (95% confidence interval (CI) 3.1-5.7%)(**Figure 2**). Restricting our analysis to only population-based studies[17,24-26,31,32,42,45,53] resulted in a similar pooled prevalence estimate of 4.1% (95%CI 2.4-6.8%).

Eight studies provided prevalence estimates stratified by age and gender.[17,18,26,38,40,43,44,47] Prevalence estimates were heterogeneous even within age and gender subgroups (**Figure 3**). Prevalence of moderate stenosis were higher in men than in women under 70 years, being on average 4.8% (95%CI 3.1-7.3%) in men and 2.2% (95%CI 0.9-4.9%) in women. In those aged over 70, prevalence estimates were higher, being on average 12.5% (95%CI 7.4-20.3%) in men and 6.9% (95%CI 4.0-11.5%) in women. One included study[47] examined a birth cohort at age 78 and had an exceptionally high prevalence estimate (22.5%; range in other studies, zero to 15.1%). Exclusion of this study altered the results in those aged over 70 to 10.7% (95%CI 6.6-16.9%) in men and 5.8% (95%CI 3.7-9.1%) in women.

Meta-regression analysis showed that both age and gender had a significant influence on the prevalence of moderate stenosis. There was an estimated increase in prevalence of moderate stenosis for older age and male gender (**Table 2**). The estimated between-study variance reduced from 0.20 to 0.10. There was no significant effect of study size, publication year, geographic region, assessment method, and study quality on moderate stenosis prevalence estimates (**Table 2**). Examination of the funnel plot (not shown) demonstrated that there was no asymmetry for studies on prevalence of moderate carotid artery stenosis (Egger's test p=0.438).

Figure 2. Prevalence of moderate asymptomatic carotid artery stenosis (≥50% stenosis). Bars indicate 95% confidence on the proportion.

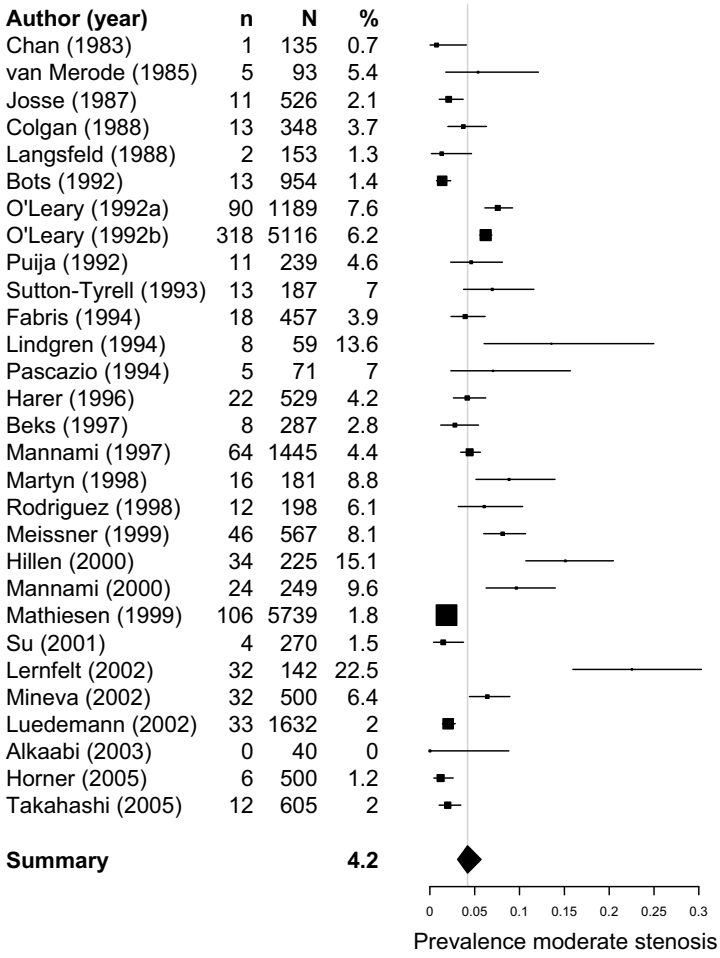

Figure 3. Prevalence of moderate asymptomatic carotid artery stenosis (≥50% stenosis) stratified by according to age and gender wherever possible. Bars indicate 95% confidence on the proportion.

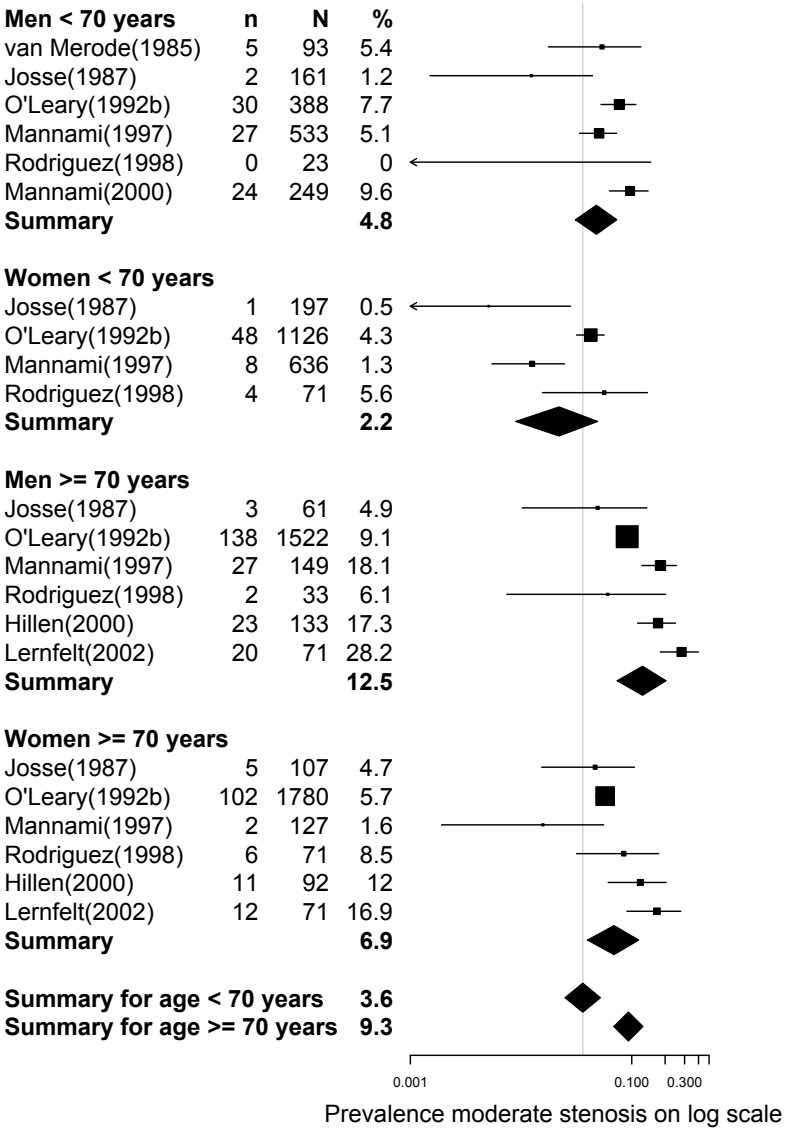

Table 2 Effect of covariates on prevalence of moderate carotid artery stenosis (random effects models).

	Estimate (SE)*	*P*-value
Univariable meta-regression analyses		
Participant characteristics		
Age	0.067 (0.017)	<0.001
Female (%)	-0.012 (0.009)	0.219
Study characteristics		
Study size		
1000 or more	Reference	
500-999	-0.285 (0.449)	0.526
less than 500	0.033 (0.393)	0.399
Publication year		
2000 or later	Reference	
1990-1999	0.298 (0.339)	0.380
before 1990	-0.592 (0.482)	0.220
Geographic region		
America	Reference	
Europe	-0.247 (0.364)	0.497
Asia	-0.396 (0.514)	0.441
Assessment method (Duplex vs. Doppler)	-0.073 (0.644)	0.910
Study quality		
Representative of general population	-0.025 (0.353)	0.943
Appropriate recruitment	0.256 (0.333)	0.443
Adequate response rate	-0.022 (0.339)	0.949
High/low study quality†	0.180 (0.339)	0.595
Multivariable meta-regression analyses		
Intercept	-7.348 (1.099)	
Age	0.080 (0.017)	<0.001
Female (%)	-0.022 (0.007)	0.003

* Parameter estimates (standard errors) are presented on a logit scale. The estimated prevalence of moderate stenosis given particular values of the covariates can be derived from the regression equation. For example, the estimated logit(prevalence) for women at age 60 is given by -7.348 + 0.080 × 60 – 0·022 × 100 = –4.71 which corresponds to a prevalence of moderate stenosis of exp(–4.71) = 0.9%.

† High quality studies had two of more of the three high quality criteria, see Methods for details.

Severe carotid artery stenosis

For the analysis of severe carotid artery stenosis (≥70%), only four studies, totaling 6,518 individuals, provided data.[36,41,45,47] Overall, the prevalence of severe stenosis ranged from zero to 4.9%, with a pooled random effects prevalence estimate of 1.7% (95%CI 0.7-3.9%). Stratified analysis and meta-regression analysis were not attempted for prevalence of severe stenosis analysis given the paucity of studies.

Discussion

We have conducted a systematic review of studies addressing the prevalence of moderate and severe carotid artery stenosis and a meta-regression analysis to understand the reasons of estimate variability. Our findings show that the prevalence of moderate stenosis increases with age in both men and women, but that men at all ages have the highest prevalence estimates. Differences age- and gender distribution across studies explained half of the heterogeneity in prevalence estimates. The number of studies that allowed meaningful data synthesis of severe stenosis was limited.

Information on the prevalence of asymptomatic carotid stenosis may provide insight into the planning and allocation of funds for screening methods to detect patients who may benefit from carotid endarterectomy. Whilst there is sufficient data to provide reliable age- and gender-specific prevalence estimates of moderate stenosis, there is limited data on prevalence estimates of severe stenosis available in the literature. At present, there is considerable variation among studies with respect to cut-off point used for severe stenosis (70%, 75%, and 80% stenosis). Moreover, the method of measurement used, i.e., NASCET or ECST, which was not always reported may also have influenced the estimates. As a result, no reliable age- and gender-specific prevalence estimates for severe stenosis could be provided, while probably only asymptomatic patients with severe stenosis are at high enough risk to justify carotid endarterectomy. [10,11,14] To resolve this lack of accurate age- and gender-specific prevalence estimates of severe stenosis, we might ask original investigators for stratified analyses for the degree of stenosis of our interest. However, in that case, we might as well ask for the individual patient data. The latter would allow recoding of variables and more flexible analyses, and more advanced modeling techniques.

We observed that moderate stenosis was more prevalent among men than among women, and there was an increasing prevalence with age, which confirms previous findings.[26,29-31,39,45] Given that carotid endarterectomy also appeared to be more beneficial in men than in women[13,14], this might imply that screening for asymptomatic carotid stenosis might be more worthwhile among men with reasonable life expectancy than among women. However, treatment choice

requires a comparison of acute treatment-related risks and future stroke risk, and only a well-designed decision analysis can gain the best possible insight in the balance of risks and benefits. Such analysis can also determine whether screening would be effective in the entire population or in subgroups according to age or gender only. Therefore, further research is required in order to identify those individuals with asymptomatic stenosis who have the most benefit from preventive treatment.

This study has several limitations. First, the stratified prevalence estimates may have been influenced by the relatively small number of studies that provided age- and gender-specific data. Another limitation concerns non-response within the included studies. As non-response increases with age, and asymptomatic carotid stenosis is more prevalent in older patients, the overall prevalence estimates may have been underestimated. Third, the studies included in this review used different methods to determine the degree of stenosis, i.e. Duplex or Doppler alone. Duplex screening has been shown to be an accurate method for assessing carotid stenosis[56] and is the most frequently used method nowadays. Doppler screening alone has been shown to be less accurate than Duplex screening and tends to underestimate the degree of stenosis. Meta-regression showed that the overall prevalence estimates of moderate stenosis, however, did not essentially differ between studies that used the Duplex assessment method or Doppler method alone. In addition, we reviewed whether the included studies reported the method of measurement of stenosis (i.e. NASCET or ECST method), since it has been shown that the NASCET method results in lower estimates of the degree of stenosis compared with the ECST method.[57] Unfortunately, only a few studies provided details about the method of measurement used. Because of the lack of information about which method of measurement is used, we were not able to convert stenosis values to one uniform method. Surprisingly, meta-regression showed that quality features did not significantly add to the variation in prevalence estimates of moderate stenosis. Our quality scoring method may, however, not have entirely captured all methodological aspects. Alternatively, the seemingly considerable number of studies (N=29) may still have been too small to yield sufficient statistical power for conducting meta-regression analyses. We think, however, that factors such as average age and gender may be much stronger determinants, i.e., may have overruled methodological quality of the studies.

In conclusion, we noted that good stratified prevalence estimations are difficult to extract from literature. Collaborative efforts with pooled analysis of individual patient data are needed to estimate the prevalence of asymptomatic carotid stenosis in subgroups more accurately. Such data can then also be used to explore whether screening and treatment of carotid artery stenosis in asymptomatic patients would be worthwhile.

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Chapter 3

Prevalence of asymptomatic carotid artery stenosis in the general population: an individual participant data meta-analysis

Abstract

Background and purpose
In the discussion on the cost-effectiveness of screening precise estimates of severe asymptomatic carotid stenosis (ACAS) are vital. Accordingly, we assessed the prevalence of moderate and severe ACAS by age and sex using pooled cohort data.

Methods
We performed an individual participant data meta-analysis (23,706 participants) of four population-based studies (MDCS, Tromsø, CAPS and CHS). Outcomes of interest were asymptomatic moderate (≥50%) and severe carotid stenosis (≥70%).

Results
Prevalence of moderate ACAS ranged from 0.2% (95% CI, 0.1% to 0.5%) in men aged below 50 years to 6.2% (4.3% to 8.9%) in men aged 80 years and above. For women this prevalence increased from zero (0.0% to 0.2%) to 5.0% (3.3% to 7.5%). Prevalence of severe ACAS ranged from 0.1% (0.0% to 0.4%) in men aged below 50 years to 1.7% (0.8% to 3.5%) in men aged 80 and above. For women this prevalence increased from zero (0.0% to 0.2%) to 1.0% (0.4% to 2.5%).

Conclusions
Prevalence of severe ACAS in the general population ranges from zero to 1.7% which is useful information in the discussion on the cost-effectiveness of screening.

Introduction

Studies have reported an annual stroke risk of approximately 2-5% for patients with severe asymptomatic carotid stenosis (ACAS)[1;2]. Two randomized controlled trials in subjects with ACAS showed a benefit from carotid endarterectomy in men[3;4], whereas uncertainty persisted in women[5]. These prompted the discussion on non-invasive screening for ACAS in the general population[5;6]. Since precise and valid prevalence estimates are important for recommendations regarding population-based screening, we initially sought to determine age- and sex-specific prevalence estimates for ACAS through systematic literature review and meta-analysis[7]. However, good stratified estimates appeared difficult to extract due to the variety in definition used for ACAS. Therefore, we set out to determine the prevalence of moderate and severe ACAS in the general population using individual participant data from four population-based cohort studies.

Methods

Data from four population-based studies of clinically asymptomatic patients were used; these cohorts have been previously detailed elsewhere[8-12]. In brief, the *Tromsø Study* is a population-based prospective study in Tromsø, Norway. All inhibitants aged 55 to 74 years and 5-10% samples of other 5-year-age groups aged ≥25 years were invited. In total 6,727 participants (attendance rate 77%) were screened and informed consent was obtained from 6,659 participants[8]. In the population-based *Malmö Diet and Cancer Study (MDCS)* a total of 28,449 participants attended between 1991 and 1996 (attendance rate 41%). A random sample of 6,103 (20%) participants had an ultrasound examination[9;10]. In the *Carotid Atherosclerosis Progression Study* (CAPS), members of a German primary healthcare scheme were invited of whom 6,962 participants (attendance rate 21%) agreed to take part[11]. The *Cardiovascular Health Study* is a community-based, prospective study of people aged ≥65 years including 5,888 subjects (attendance rate 57%)[12].

The following baseline characteristics were recorded: age, sex, history of vascular disease, body mass index (BMI), waist-hip ratio (WHR), blood pressure, hypertension, diabetes mellitus, smoking status, blood lipids and methods of measuring stenosis. Hypertension was defined as ≥140/90 mmHg or treatment with antihypertensive drugs. Diabetes mellitus was defined as fasting blood glucose level ≥7mmol/l or treatment with insulin or oral glucose-lowering drugs. Hyperlipidemia was defined as total cholesterol ≥4.5 mmol/L, LDL-cholesterol

≥2.5mmol/L or use of lipid-lowering medication[13]. Moderate ACAS was defined as ≥50% stenosis and severe ACAS as ≥70% stenosis, measured by Doppler ultrasonography supported by B-mode sound imaging in three of the four studies (**Table 1**). When both carotid arteries were measured, we used the largest stenosis observed[14].

We determined the prevalence of moderate and severe ACAS, by age and sex in the complete dataset and among those without a history of coronary heart disease or cerebrovascular disease. Analysis of variance was used to estimate age- and sex-specific prevalence estimates adjusted for hypertension, hyperlipidemia, diabetes mellitus and smoking. We assessed whether the overall prevalence estimates differed among current smokers, hyperlipidemic, hypertensive and diabetic subjects or the combination of one or more of these vascular risk factors compared to those without risk factors.

Results

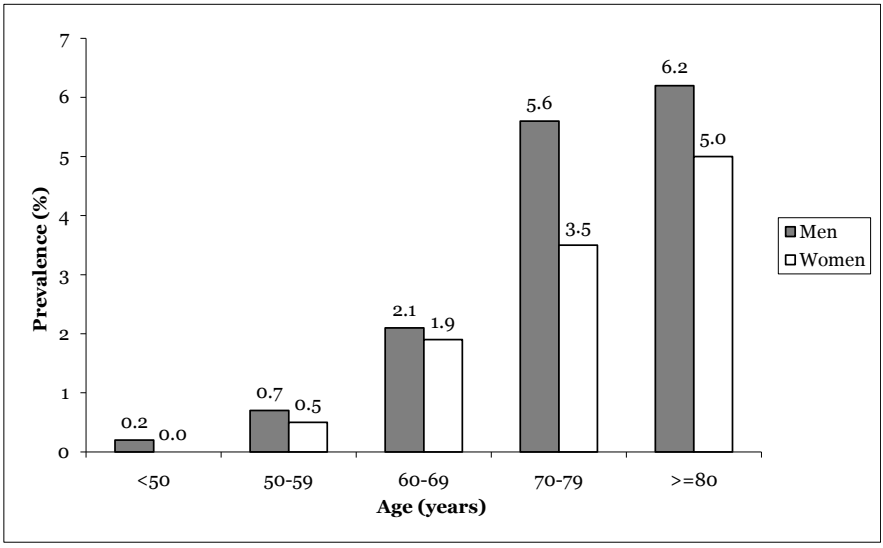
General characteristics are shown in **Table 1**. In men the prevalence of moderate ACAS increased with age from 0.2% (95% Confidence Interval, 0.1% to 0.5%) to 6.2% (4.3% to 8.9%) for severe ACAS the prevalence increased from 0.1% (0.0% to 0.4%) to 1.7% (0.8% to 3.5%) **(Figure 1 and Webtable 1).** For women, the prevalence of moderate ACAS increased from zero (0.0% to 0.2%) to 5.0% (2.3% to 7.5%); for severe ACAS this prevalence increased from zero (0.0% to 0.2%) to 1.0% (0.4% to 2.5%). The prevalence estimates were almost similar until the age of 79 years, in participants without a history of vascular disease, when the age was 80 and above the prevalence of severe stenosis differed **(Webtable 2)**. The prevalence of severe ACAS was higher in participants with vascular risk factors **(Figure 2)**.

Table1. General characteristics of the study population, by cohort.

	Tromsø	MDCS	CAPS	CHS	Total
Nr. of participants	6659	6103	5056	5888	23706
Mean age, y *(sd)*	60.2 *(10.1)*	57.5 *(5.9)*	50 *(13.1)*	72.8 *(5.6)*	60.5 (12.1)
Male sex, n (%)	3298 (49.5)	2572 (42.1)	2471 (48.9)	2495 (42.4)	10836 (45.7)
History of disease, n (%)					
Coronary heart disease, n (%)	822 (12.3)	102 (1.7)	108 (2.1)	1154 (19.6)	2186 (9.2)
Cerebrovascular disease, n (%)	182 (2.7)	69 (1.2)	52 (1.0)	349 (5.9)	652 (2.8)
Body Mass Index mean kg/m2 *(sd)*	26.1 *(3.9)*	25.9 *(4.0)*	26.6 *(4.1)*	26.7 *(4.7)*	26.3 (4.2)
Waist-Hip Ratio, mean *(sd)*	0.87 *(0.08)*	0.85 *(0.09)*	0.95 *(0.11)*	0.93 *(0.09)*	0.9 (0.1)
Hypertension, n (%)	2257 (33.9)	2659 (43.6)	707 (14.0)	2511 (42.6)	7760 (32.7)
Mean systolic BP *(sd)*	145 (22.5)	141 (19)	128 (17)	136.5 *(21.8)*	141.2 (21.5)
Mean Diastolic BP, *(sd)*	83 (12)	87 (9.5)	77.3 (10.1)	70.7 *(11.4)*	79.9 (12.8)
Diabetes, n (%)	217 (3.3)	157 (2.6)	134 (2.7)	722 (12.3)	1230 (5.2)
Smoker, n (%)	2116 (31.8)	1618 (28.1)	1055 (20.9)	700 (11.9)	5489 (23.2)
Lipids, mean *(sd)*					
Total Cholesterol	6.75 *(1.29)*	6.2 *(1.1)*	NR	5.4 *(1.1)*	6.1 *(1.3)*
HDL Cholesterol	1.5 *(0.43)*	1.4 *(0.4)*	1.54 *(0.44)*	1.37 *(0.37)*	1.46 *(0.42)*
LDL Cholesterol	NR	4.2 *(1.0)*	3.35 *(0.93)*	4.16 *(0.98)*	3.6 *(1.02)*
Triglycerides	1.7 *(1.1)*	1.4 *(0.8)*	1.5 *(0.99)*	1.37 *(0.8)*	1.55 *(0.95)*
Methods of measure stenosis					
Duplex Ultrasonography	yes	yes	yes	no	
-Lumen diameter method	yes	yes	no	.	
-Cross sectional lumen method	yes	no	yes	.	

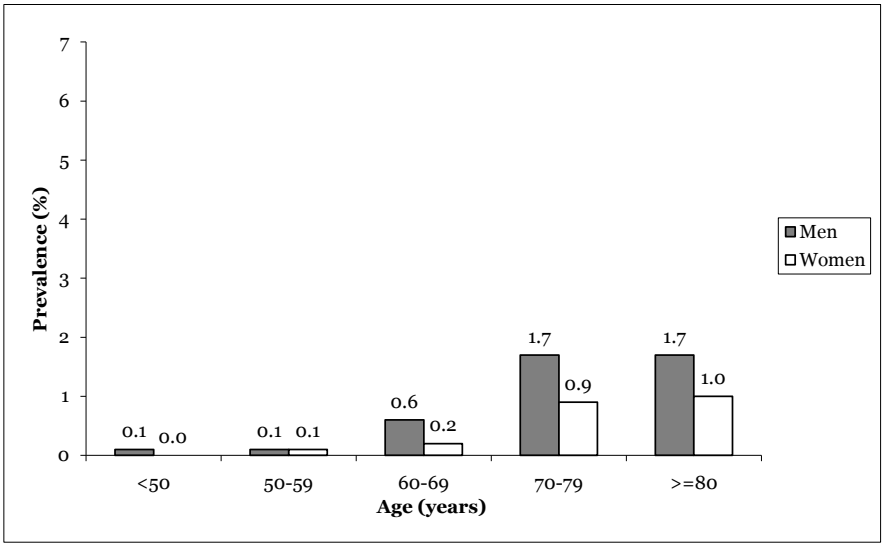
NR=Not Reported, MDCS = Malmö Diet and Cancer Study, CAPS = Carotid Atherosclerosis Progression Study, CHS = Cardiovascular Health Study, HDL = high density lipoprotein, LDL = low density lipoprotein

Figure 1. A The prevalence of moderate stenosis in men and women



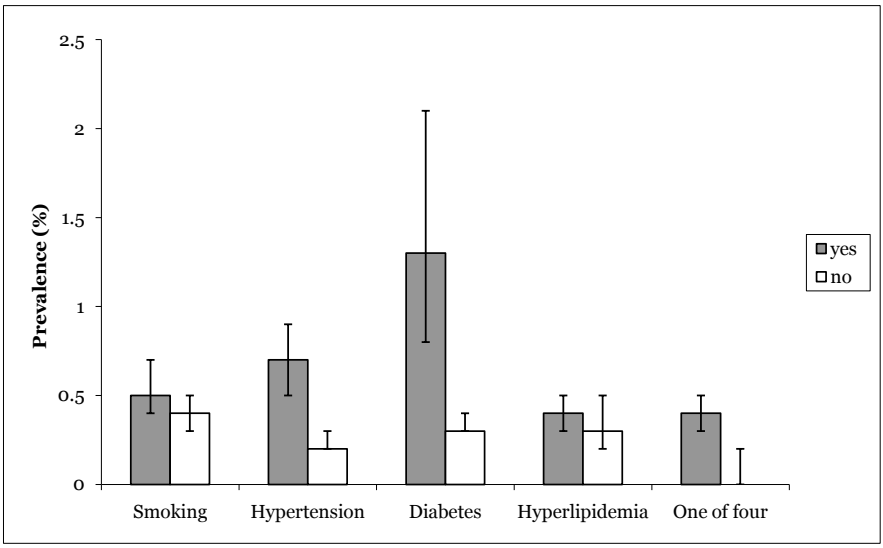
Adjusted for smoking, hypertension, hyperlipidemia and diabetes.

B The prevalence of severe stenosis in men and women.



Adjusted for smoking, hypertension, hyperlipidemia and diabetes.

Figure 2. The prevalence of moderate stenosis in subgroups



Discussion

The prevalence of moderate ACAS varied from zero to 6.2% and the prevalence of severe ACAS from zero to 1.7%. Prevalence estimates increased with age and were slightly higher in men.

Age- and sex-specific estimates in the present study are smaller than the prevalence estimates reported in our previous literature-based meta-analysis[7]. This differences in prevalence may have been introduced by the selection process of individual papers in the literature-based meta-analysis. Only a few studies reported age- and sex-specific data[7]. Also, it was not possible to correct for heterogeneity in baseline characteristics between studies. These aspects were overcome in the present analyses in which a large number of persons was involved, giving us the ability to present precise estimate of the ACAS prevalence by age and sex. This study has some limitations. Our meta-analysis suffers from non-participation in the individual cohorts. When non-response is related to the more sick or high-risk patients, which is supported by the non-participant analyses in the MDCS cohort[15], our estimates reflect an underestimation of the actual ACAS prevalence. The volunteer approach in CAPS, however, did not select participants with a particularly low vascular risk[16]. Although, differences exist in the methods for determination of stenosis-degree between studies [9-13], the regression analyses

using the Tromso data indicated that different approaches were unrelated to the prevalence estimate of moderate ACAS. Therefore, it is unlikely that the different methods used to measure stenosis degree have affected our results.

For the discussion about the feasibility and cost-effectiveness of screening the general population for ACAS, our findings are important. Some reported that screening for severe ACAS was cost-effective when the prevalence of severe ACAS was at least 20%[17]. Using that cut-off point and given our estimates, population screening is unlikely to become worthwhile. Yet, we recommend the development of a prediction rule estimating the risk of having severe carotid stenosis to evaluate whether we can select a high risk group of participants that might benefit from screening.

In conclusion, overall the prevalence of severe ACAS in the general population ranges from zero to 1.7%. Its prevalence increases with age and with risk factor levels. These results are of relevance for the discussion on screening for severe asymptomatic carotid artery stenosis.

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Webtable 1. Prevalence of moderate stenosis and severe stenosis by age and sex, adjusted for hypertension, hyperlipidemia, smoking and diabetes

Men	Total	>=50%		>=70%		**Women**	Total	>=50%		>=70%	
Age (years)	N	n (%)	*95% CI*	n (%)	*95% CI*	Age (years)	N	n (%)	*95% CI*	n (%)	*95% CI*
<50	1931	4 (0.2)	*0.1 to 0.5*	2 (0.1)	*0.0 to 0.4*	<50	1923	0 (0.0)	*0.0 to 0.2*	0 (0.0)	*0.0 to 0.2*
50-59	2579	18 (0.7)	*0.4 to 1.1*	3 (0.1)	*0.0 to 0.3*	50-59	2869	14 (0.5)	*0.3 to 0.8*	3 (0.1)	*0.0 to 0.3*
60-69	3407	72 (2.1)	*1.7 to 2.6*	20 (0.6)	*0.4 to 0.9*	60-69	4407	84 (1.9)	*1.5 to 2.3*	9 (0.2)	*0.1 to 0.4*
70-79	1994	112 (5.6)	*4.7 to 6.7*	34 (1.7)	*1.2 to 2.4*	70-79	2478	87 (3.5)	*2.8 to 4.3*	22 (0.9)	*0.6 to 1.4*
>=80	414	26 (6.2)	*4.3 to 8.9*	7 (1.7)	*0.8 to 3.5*	>=80	432	22 (5.0)	*3.3 to 7.5*	4 (1.0)	*0.4 to 2.5*
Overall	10325	232 (2.2)	*2.0 to 2.6*	66 (0.6)	*0.5 to 0.8*	Overall	12109	207 (1.7)	*1.5 to 2.0*	38 (0.3)	*0.2 to 0.4*

Webtable 2. Prevalence of moderate and severe stenosis by age and sex in participants without history of coronary or cerebrovascular disease, adjusted for hypertension, hyperlipidemia, smoking and diabetes

Men	Total	>=50%		>=70%		**Women**	Total	>=50%		>=70%	
Age (years)	N	n (%)	*95% CI*	n (%)	*95% CI*	Age (years)	N	n (%)	*95% CI*	n (%)	*95% CI*
<50	1909	4 (0.2)	*0.1 to 0.5*	2 (0.1)	*0.0 to 0.4*	<50	1915	0 (0.0)	*0.0 to 0.2*	0 (0.0)	*0.0 to 0.2*
50-59	2405	17 (0.7)	*0.4 to 1.1*	5 (0.2)	*0.1 to 0.5*	50-59	2798	11 (0.4)	*0.2 to 0.7*	3 (0.1)	*0.0 to 0.3*
60-69	2235	27 (1.2)	*0.8 to 1.7*	4 (0.2)	*0.1 to 0.5*	60-69	2942	32 (1.1)	*0.8 to 1.5*	3 (0.1)	*0.0 to 0.3*
70-79	475	28 (5.9)	*4.1 to 8.4*	12 (2.5)	*1.4 to 4.3*	70-79	595	15 (2.6)	*1.6 to 4.2*	6 (1.0)	*0.5 to 2.2*
>=80	14	1 (7.2)	*1.3 to 31.5*	1 (7.2)	*1.3 to 31.5*	>=80	26	1 (4.0)	*0.7 to 19.1*	0 (0.0)	*0.0 to 12.9*
Overall	7038	74 (1.1)	*0.9 to 1.4*	24 (0.3)	*0.2 to 0.5*	Overall	8276	59 (0.7)	*0.6 to 0.9*	12 (0.1)	*0.1 to 0.3*

Chapter 4

Cost-effectiveness of one-time screening for asymptomatic carotid artery stenosis in the general population

Abstract

Objective
Since trials have shown that for certain groups carotid endarterectomy in case of high grade stenosis is beneficial, the question whether population-based screening for ACAS is actually warranted has raised much discussion.
The aim of the current analysis is to evaluate the factual cost-effectiveness screening for ACAS by Duplex followed by carotid computer tomography angiograph (CTA) and subsequent endarterectomy in the general population.

Method
A Markov model (Monte Carlo Simulation) simulating the histories of cohorts of patients according to prevalence distribution of grade of stenosis (<70% and 70-99%), age (55, 65 and 75 years), gender and co-morbidity was developed reflecting National survival statistics and stroke occurrence. Costs, effects in terms of stroke and overall survival and utility estimates were literature based. Screening was considered cost-effective at an incremental cost-effectiveness ratio of €20,000 euro per QALY gained.

Results
The prevalence cut-off value when screening is cost-effective varied with age and sex, it was cost-effective to screen for severe ACAS in 65 year-old men with a prevalence of ACAS of at least 3%. In 75-year-old men screening was cost-effective for a prevalence of at least 3%. In 55-year-old men screening was not cost-effective. In 75-year-old women screening appeared cost-effective when the prevalence surpassed 5%. In 55- and 65-year old women screening was not cost-effective.

Conclusion
These results corroborate the notion that in middle aged and elderly adults screening may only be warranted in subgroups with a relatively high prevalence of ACAS. Presently, such subgroups are not well identified.

Introduction

The issue of screening for asymptomatic carotid artery stenosis (ACAS) has become opportune since the benefit of carotid endarterectomy for patients with severe asymptomatic carotid artery stenosis has been demonstrated[1;2]. In many countries surgery (or carotid endarterectomy) for severe asymptomatic carotid artery stenosis is supported by best practice guidelines[3;4]. Many factors, however, affect the potential utility of screening in an asymptomatic population. The overall benefit of screening depends on the prevalence of the disease, the sensitivity and specificity of the screening tool, the complication rate of the reference test, the complication rate of the treatment and the benefits of the treatment in terms of event reduction[5]. Previously, it was suggested that screening would be cost-effective in populations with a prevalence of severe ACAS of at least 20%[1]. These studies combined Duplex as a screening tool with other (invasive) tests to confirm stenosis. Since new evidence and diagnostic possibilities, i.e., Duplex followed by computer tomography angiography[6], have become available cost-effectiveness should be re-evaluated.

Recent guidelines advise screening for ACAS in high-risk populations such as patients undergoing open heart surgery including coronary artery bypass surgery; patients with peripheral vascular diseases, patients following carotid endarterectomy, or carotid artery stent placement; and patients with a family history of vascular diseases and hyperhomocysteinemia[7].

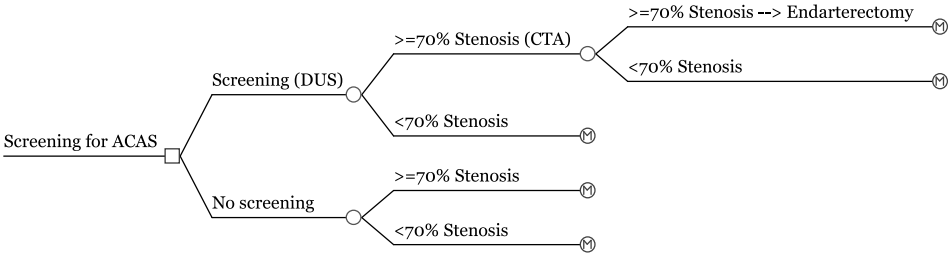
We previously opened the discussion on the topic of screening for ACAS and carotid endarterectomy in the general population[8] as the claims regarding benefits of treatment in the general population seemed to be preliminary and based on studies that were not population-based[9;10]. The aim of the current analysis is to evaluate the factual cost-effectiveness of screening for ACAS by Duplex followed by CTA and endarterectomy in the general population.

Methods

Model

We developed a Markov model and used Monte Carlo simulation to estimate the long-term effects of screening for carotid artery stenosis with Duplex. The principle of a Markov model is that it defines a number of discrete health states and it assumes that at any point in time a person is in one of these health states. During a model cycle (i.e. one year in this study) persons can move from one health state to another as defined by transition probabilities. We defined five health states: healthy, post minor stroke, post major stroke, post myocardial infarction and death and a transition state stroke after carotid endarterectomy. **Figure 1** shows the general structure of the model. The model was designed to simulate cohorts of thus far asymptomatic men and women.

Figure 1. General structure of the Markov Model.
ACAS = Asymptomatic carotid artery stenosis



DUS = Duplex Ultrasound
CTA = Carotid computer tomography angiograph

Screening arm

In the screening arm all subjects underwent a Duplex examination. If the Duplex was positive for severe stenosis (≥70%, true positive or false positive) disease would be confirmed with computed tomographic angiography (CTA). The number of patients that underwent a CTA was a function of the prevalence of severe carotid artery stenosis and the sensitivity and specificity of the Duplex for assessment of severe stenosis. We assumed that CTA is safe i.e., has no risk of complications. If CTA confirms a severe stenosis patients underwent carotid endarterectomy (CEA). Patients who underwent CEA may experience a complication and as a result die during or immediately after the intervention ("death" state), or survive with mild or moderate to severe disability ("stroke" state), or survive without complications and have normal neurological function ("no event" state). In the

5 years after surgery a small risk of stroke would remain and patients could die from stroke or other causes.

No screening arm
The no-screening arm did not include the initial Duplex screening, and obviously an underlying risk of stroke persisted. Also, patients could die from stroke or other causes in subsequent years.

Variables
Input parameters, including transition probabilities, treatment effects of CEA and utilities for 65-year-old-men and women are shown in **Table 1**. Because the model cycle is one year, transition probabilities reflect annual incidence rates for the events of interest (i.e. stroke or myocardial infarction). Most parameters were derived from literature, see **Table 1**. Based on the stroke incidence among patients in the carotid endarterectomy trials[9;10] we assumed that people with severe asymptomatic stenosis had a five times higher risk compared to people without severe asymptomatic stenosis. The risks and benefits of carotid endarterectomy to prevent stroke for patients with asymptomatic carotid artery stenosis have been shown in two large trials, ACAS and ACST[9;10]. The benefit of carotid endarterectomy was initially assumed to last for five years[11].

Costs
We evaluated the direct medical costs. Event-related costs in the first year and ongoing costs were distinguished because health care costs immediately after an event are higher than in the subsequent years after an event. The costs of Duplex, CTA, CEA, stroke care during the first year, chronic care during subsequent years and the costs of death were extracted from literature [12;13]. All costs estimates were updated to 2008 with the Dutch inflation indices[14] and calculated in Euros.

Analysis
Life-years, QALYs and costs were calculated over a lifetime horizon. Incremental cost-effectiveness ratios (iCERs) were defined as the difference in costs divided by the difference in QALYs. Screening was considered cost-effective up to an incremental cost-effectiveness ratio of 20,000 Euros per QALY gained[15]. All analyses were conducted in hypothetical cohorts of 100,000 men and women aged 55, 65 or 75 years with increasing prevalence of severe asymptomatic carotid stenosis (1%, 3%, 5%, 10%, 15%, 20%, 25% and 30%). The costs and benefits were both discounted with four percent. Sensitivity analyses were performed to

evaluate the effect of varying the input parameters over the range given in **Table 1**. Additionally, we evaluated the following scenarios: 1) costs were discounted at 4% and benefits at 1.5% in accordance with current Dutch guidelines[16] 2) costs and benefits were not discounted 3) we corrected for the competing mortality and morbidity in men and women with severe asymptomatic carotid artery stenosis by multiplying the stroke risks and the risk of dying both by a factor two 4) we changed the 5 year benefit from endarterectomy into 3 year benefit, because the benefits of endarterectomy is only known for three years[11] 5) we changed the 5 year benefit from endarterectomy into life-time benefit, which will be highly uncommon 6) we added 20% non-compliance to screening i.e. participants were invited but did not come to the screening 7) we added 20% non-compliance to endarterectomy i.e. participants went to the screening, a stenosis of more than 70% was found, but did not go to surgery 8) we added 20% non-compliance to both, screening and the endarterectomy.

To assess the uncertainty around the modelled output, we performed probabilistic sensitivity analyses with Monte Carlo simulation. We evaluated the clinical courses of 100,000 hypothetical people for both strategies (screening versus no screening) 500 times, with each simulation involving a random draw from each of the input parameter distributions given in **Table 1**. Multiple outputs were thus calculated[17].

Table 1. Estimates used in the model.

Paremeters	*Men, estimate (range)*	*Women, estimate (range)*	*Distribution*	*Reference*
Overall one year mortality rate (per 100,000 person years)	1994 (1899-2089)	1010 (945-1075)		14
Stroke				
Incidence general population (per 100,000 person years)	551 (524-579)	339 (319-360)	Beta	21
Incidence severe stenotic population (per 100,000 person years)	1696 (1631-1761)	1696 (1631-1761)	Beta	21
Case fatality of stroke (%)	24 (22-26)	26 (23-29)	Beta	21
Relative risk of stroke in severe stenotic population	5.0 (4.0-6.0)	5.0 (4.0-6.0)	Log linear	9;10
Screening				
Sensitivity Duplex Ultrasound (70% stenosis)	86 (84-89)	86 (84-89)	Triangular	22
Specificity Duplex Ultrasound (70% stenosis)	87 (84-90)	87 (84-90)	Triangular	22
Intervention risks				
Perioperative strokes after CEA	0.009 (0.006-0.019)	0.019 (0.011-0.030)	Beta	9;10
Perioperative mortality after CEA	0.005 (0.002 -0.009)	0.009 (0.005-0.019)	Beta	9;10
Intervention benefits				
Relative risk of stroke after CEA	0.37 (0.27-0.50)	0.51 (0.33-0.79)	Log linear	9;10
Utilities				
Utility after stroke	0.62 (0.60-0.78)	0.62 (0.60-0.78)	Triangular	23
Utility after MI	0.88 (0.80-0.95)	0.88 (0.80-0.95)	Triangular	24
Costs				
Doppler Ultrasonography	60			12
CTA	290			13
Carotid endarterectomy	3457			12
Chronic care for minor stroke during 1st year	6383			12
Chronic care for minor stroke during subseqent years	1092			12
Chronic care for major stroke during 1st year	36400			12
Chronic care for major stroke during subseqent years	21254			12
Chronic care for MI during 1st year	15330			25
Chronic care for MI during subseqent years	996			26
Death	2715			12

Results

Health Outcomes

The number and type of events for hypothetical cohorts of 100,000 men and women aged 55, 65 and 75 years with increasing prevalence of severe carotid artery stenosis in both the screening arm and no-screening arm are presented in **Table 2 and Table 3**. Screening resulted in health benefits in men of all ages. In 55-year-old men this benefits ranged from 0.001 QALY when the prevalence of severe ACAS was 1% to 0.021 QALY when the prevalence was 30%. In 75-year-old men health benefits increased from 0.004 to 0.121 QALYs **(Table 2)**.

Screening resulted in QALY loss in women aged 55 years. In 65-year-old women health benefits ranged from 0.001 QALY when the prevalence of severe ACAS of 3% to 0.006 QALY when the prevalence of severe ACAS was 30%. In 75-year-old women the QALY gain ranged from 0.002 QALY when the prevalence of severe ACAS was 1% to 0.068 QALY when the prevalence of severe ACAS was 30% **(Table 3)**.

Costs and incremental cost-utility ratios

Mean life-time costs of screening a 55-year-old man ranged from 6,000 euros to 9,300 euros. The incremental cost effectiveness ratio (iCER) thus ranged from 170,000 euro when the prevalence of severe ACAS was 1% to 34,000 euros when the prevalence of ACAS was 30%. Accordingly, using a cut-off point of 20,000 euros screening was not cost-effective for men aged 55. In 65-year-old men the mean lifetime cost of screening ranged from 5,700 euros to 8,500 euros. The iCER ranged from 49,000 euros to 6,500 euro per QALY gained. In men aged 65 screening appeared cost-effective from a prevalence of 3% onward.

Mean life time costs of screening 75-year-old men ranged from 4,600 euros to 6,400 euros. The iCER ranged from 27,000 euro per QALY gained to 3,700 euros per QALY gained. Screening was cost-effective when the prevalence exceeded 3% in men aged 75 **(Table 2)**.

For women, screening was only cost-effective in women aged 75 with a prevalence above 5% **(Table 3)**.

Table2: Quality adjusted life expectancy and costs of screening versus no screening on cohorts of Dutch men of different ages and with different prevalences of severe ACAS over a life-time period.

Table2: Quality-adjusted life expectancy and costs of screening versus no screening on cohorts of Dutch men of different ages and with different prevalences of severe ACAS over a life-time period.

		Precentage Major Stroke			Percentage Minor Stroke			QALY			Costs			
Age (yrs.)	**Prev.**	**No Screening**	**Screening**	**Difference**	**No Screening**	**Screening**	**Difference**	**Screening**	**No Screening**	**Difference**	**Screening**	**No Screening**	**Difference**	**iCER**
55	1.0%	5.1%	5.1%	0.0%	10.3%	10.3%	0.0%	13.930	13.929	0.001	5884	5765	118	172091
	3.0%	5.4%	5.3%	0.0%	10.7%	10.7%	0.0%	13.906	13.904	0.002	6119	5960	159	77235
	5.0%	5.6%	5.5%	0.0%	11.2%	11.1%	0.1%	13.882	13.879	0.003	6355	6155	200	58264
	10.0%	6.1%	6.1%	0.1%	12.3%	12.1%	0.1%	13.822	13.815	0.007	6945	6643	302	44036
	15.0%	6.7%	6.6%	0.1%	13.4%	13.2%	0.2%	13.763	13.752	0.010	7535	7130	405	39293
	20.0%	7.2%	7.1%	0.1%	14.5%	14.2%	0.3%	13.703	13.689	0.014	8125	7618	507	36922
	25.0%	7.8%	7.6%	0.2%	15.6%	15.3%	0.3%	13.643	13.626	0.017	8715	8105	609	35499
	30.0%	8.4%	8.2%	0.2%	16.7%	16.3%	0.4%	13.583	13.563	0.021	9305	8593	712	34550
65	1.0%	5.0%	5.0%	0.0%	10.0%	10.0%	0.0%	10.277	10.275	0.002	5681	5572	109	48988
	3.0%	5.2%	5.2%	0.1%	10.5%	10.4%	0.1%	10.254	10.248	0.007	5873	5741	132	**19718**
	5.0%	5.5%	5.4%	0.1%	10.9%	10.8%	0.2%	10.231	10.220	0.011	6065	5910	154	13865
	10.0%	6.0%	5.8%	0.2%	12.0%	11.7%	0.3%	10.173	10.151	0.022	6544	6333	211	9474
	15.0%	6.6%	6.3%	0.3%	13.1%	12.6%	0.5%	10.115	10.081	0.033	7023	6756	267	8011
	20.0%	7.1%	6.8%	0.3%	14.2%	13.6%	0.7%	10.057	10.012	0.045	7502	7178	324	7279
	25.0%	7.7%	7.3%	0.4%	15.3%	14.5%	0.8%	9.999	9.943	0.056	7981	7601	381	6840
	30.0%	8.2%	7.7%	0.5%	16.4%	15.4%	1.0%	9.940	9.874	0.067	8461	8023	437	6547
75	1.0%	4.7%	4.7%	0.0%	9.4%	9.4%	0.1%	6.749	6.745	0.004	4596	4486	109	27058
	3.0%	4.9%	4.8%	0.1%	9.9%	9.7%	0.2%	6.731	6.719	0.012	4722	4590	132	10925
	5.0%	5.1%	5.0%	0.2%	10.3%	10.0%	0.3%	6.713	6.693	0.020	4848	4693	155	7698
	10.0%	5.7%	5.3%	0.3%	11.4%	10.7%	0.7%	6.667	6.627	0.040	5164	4951	213	5279
	15.0%	6.2%	5.7%	0.5%	12.4%	11.4%	1.0%	6.622	6.561	0.061	5480	5209	271	4472
	20.0%	6.8%	6.1%	0.7%	13.5%	12.2%	1.3%	6.577	6.496	0.081	5795	5467	329	4069
	25.0%	7.3%	6.5%	0.8%	14.6%	12.9%	1.7%	6.531	6.430	0.101	6111	5725	386	3827
	30.0%	7.8%	6.8%	1.0%	15.7%	13.7%	2.0%	6.486	6.364	0.121	6427	5983	444	3665

Table3: Quality adjusted life expectancy and costs of screening versus no screening on cohorts of Dutch women of different ages and with different prevalences of severe ACAS over a life-time period.

Quality adjusted life expectancy and costs of screening versus no screening on cohorts of Dutch women of different ag
different prevalences of severe ACAS over a life-time period.

		Precentage Major Stroke			Percentage Minor Stroke			QALY			Costs			
Age (yrs.)	**Prev.**	**No Screening**	**Screening**	**Difference**	**No Screening**	**Screening**	**Difference**	**Screening**	**No Screening**	**Difference**	**Screening**	**No Screening**	**Difference**	**iCER**
55	1.0%	6.2%	6.2%	0.0%	12.4%	12.4%	0.0%	15.897	15.898	-0.001	4757	4623	134	-114789
	3.0%	6.4%	6.4%	0.0%	12.9%	12.9%	0.0%	15.869	15.872	-0.004	5015	4808	207	-59065
	5.0%	6.7%	6.7%	0.0%	13.4%	13.3%	0.0%	15.840	15.846	-0.006	5274	4993	280	-47920
	10.0%	7.3%	7.3%	0.0%	14.6%	14.6%	0.0%	15.769	15.781	-0.012	5919	5456	462	-39561
	15.0%	7.9%	7.9%	0.0%	15.8%	15.8%	0.1%	15.698	15.715	-0.018	6564	5919	645	-36775
	20.0%	8.5%	8.5%	0.0%	17.1%	17.0%	0.1%	15.626	15.650	-0.023	7209	6382	827	-35382
	25.0%	9.1%	9.1%	0.1%	18.3%	18.2%	0.1%	15.555	15.584	-0.029	7854	6844	1009	-34546
	30.0%	9.8%	9.7%	0.1%	19.5%	19.4%	0.1%	15.484	15.519	-0.035	8499	7307	1192	-33989
65	1.0%	6.2%	6.2%	0.0%	12.3%	12.3%	0.0%	12.492	12.492	0.000	5139	5016	124	670880
	3.0%	6.4%	6.4%	0.0%	12.8%	12.8%	0.0%	12.461	12.460	0.001	5373	5196	176	318155
	5.0%	6.7%	6.6%	0.0%	13.3%	13.3%	0.1%	12.430	12.429	0.001	5606	5377	229	247610
	10.0%	7.3%	7.2%	0.1%	14.6%	14.4%	0.1%	12.351	12.349	0.002	6188	5829	360	194701
	15.0%	7.9%	7.8%	0.1%	15.8%	15.6%	0.2%	12.272	12.270	0.003	6771	6281	490	177065
	20.0%	8.5%	8.4%	0.1%	17.0%	16.8%	0.3%	12.194	12.190	0.004	7354	6733	621	168247
	25.0%	9.1%	9.0%	0.2%	18.3%	17.9%	0.4%	12.115	12.111	0.005	7937	7185	752	162956
	30.0%	9.8%	9.5%	0.2%	19.5%	19.1%	0.4%	12.037	12.031	0.006	8520	7636	883	159429
75	1.0%	5.9%	5.9%	0.0%	11.8%	11.8%	0.0%	8.592	8.590	0.002	4584	4467	117	51699
	3.0%	6.2%	6.1%	0.1%	12.3%	12.2%	0.1%	8.563	8.556	0.007	4752	4594	157	23040
	5.0%	6.4%	6.3%	0.1%	12.8%	12.6%	0.2%	8.535	8.523	0.011	4919	4722	197	**17308**
	10.0%	7.0%	6.8%	0.2%	14.0%	13.7%	0.4%	8.463	8.440	0.023	5337	5041	296	13010
	15.0%	7.6%	7.4%	0.3%	15.3%	14.7%	0.6%	8.391	8.357	0.034	5755	5361	395	11577
	20.0%	8.3%	7.9%	0.4%	16.5%	15.8%	0.8%	8.320	8.274	0.045	6174	5680	494	10860
	25.0%	8.9%	8.4%	0.5%	17.7%	16.8%	0.9%	8.248	8.191	0.057	6592	5999	593	10430
	30.0%	9.5%	8.9%	0.6%	19.0%	17.8%	1.1%	8.176	8.108	0.068	7010	6318	692	10144

***NA=not applicable**

Sensitivity analyses

Sensitivity analyses and scenario-analyses were performed in 65-year-old-men with a prevalence of ACAS of 3%. Uncertainty in the possibility of having a fatal or non-fatal stroke contributed most to the costs of screening and uncertainty around the utility of having a major or minor stroke contributed the most to the health benefits of screening. Sensitivity analysis also showed that even though the point estimate of a 65-year-old cohort of men with a prevalence of ACAS of 3% indicated screening would be cost-effective, there would still be a 25% chance that screening resulted in QALY loss **(Figure 2)**.

The results of the scenario-analyses are presented in **Table 4.** In our base case scenario, screening 65-year-old men with a prevalence of 3% increased mean QALYs (10.254 vs 10.248) at a higher cost (€ 5,873 vs € 5,741). The costs per additional QALY were €19,700. When the benefits were discounted with 1.5% and the costs with 4%, the iCER decreased to €15,600 per QALY. When the benefits and costs were not discounted the iCER was 11,700 euros per QALY. When we corrected for competing mortality and morbidity there was no change in costs but the QALY difference was lower resulting in an iCER of 29,000 euro per QALY gained. When we changed the 5 year benefit from carotid endarterectomy into a 3 year benefit, the QALY gain was twice as small. The resulting iCER was 47,000 euro per QALY gained. When the 5-year benefit from endarterectomy was changed into life-time benefit, screening became very cost-effective. The iCER was 1710 euro per QALY gained. When we added non compliance to screening the costs were less than the base-case scenario, but the QALY gain was also smaller, resulting in an iCER of 22,000 euro per QALY gained. Adding non-compliance to endarterectomy resulted in an iCER of 24,000 euro per QALY gained and adding non compliance to both, screening and endarterectomy resulted in an ICER of 27,000 euro per QALY gained.

Figure 2. Monte Carlo simulation results for a hypothetical cohort 65 year-old men with a prevalence of severe ACAS of 3%, plotted on a cost-effectiveness-plane.

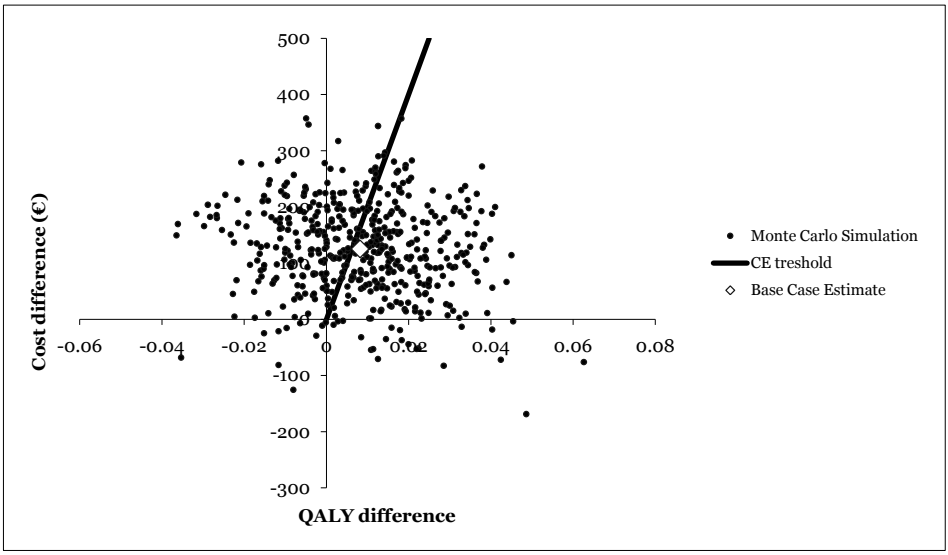


Table4; Scenario-analysis examining incremental cost-effectivenss ratio in hypothetical cohort of 65-year-old men with a prevalence of ACAS of 3%.

	Difference in QALY	Difference in Costs (€)	iCER
Base-case scenario	0.007	132	19718
Discounting effects with 1.5% and costs with 4%	0.008	132	15563
No discounting	0.010	115	11676
Competing mortality and morbidity	0.005	132	28963
3 year effect of endarterectomy	0.003	158	47862
Life-Time effect of endarterectomy	0.024	41	1710
Non Compliance Screening	0.005	117	21965
Non Compliance Endarterectomy	0.005	126	23769
Non Compliance Screening and Endarterectomy	0.004	113	26591

Discussion

Our analyses showed that for 65-year-old men with a prevalence of ACAS of 3% or higher, one-time screening for ACAS increased QALYs at acceptable cost. For women screening was cost-effective when the age was 75 years and the prevalence was 5% or higher. In 75-year-old men screening was cost-effective, when the prevalence of ACAS was 3% or above. Pooled prevalence of severe asymptomatic carotid artery stenosis in the general population was only 1.7%[18].

Previous cost-effectiveness analyses indicated that one-time screening was cost-effective in men but only at a prevalence of severe carotid artery stenosis of 20%[1;2]. The observed health benefit was small, but significant, and applied to men only. These findings were based on the results of a single trial, the ACAS. Others also reported that non-invasive screening in asymptomatic patients with an elevated risk of carotid artery disease, e.g. patients with a carotid bruit, might be beneficial if the prevalence of operable lesions would be 20% or higher[19]. However, it seems quite unlikely that a subgroup with such a high prevalence of severe asymptomatic carotid arterial stenosis[1;19] can be identified easily. Therefore, screening a priori seemed ineffective. Importantly, in previous cost-effectiveness studies conventional carotid angiography was used to confirm the positive test result of the Duplex examination[1;2;19]. However, angiography may not be current practice anymore in many clinics. Also, conventional angiography is more expensive and carries an inherent risk of complication. Particularly the latter is an important distinction from other non-invasive screening tools with similar sensitivity and specificity. As a result previous cost-effectiveness estimates have become outdated.

An important drawback of previous studies was that variability in prevalence of stenosis was not accounted for, nor was competing morbidity and mortality [2]. The latter is of course particularly important with increasing age.

Moreover, women were not specifically studied in prior studies. We found that the cost-effectiveness of screening was different from that in men. Screening appeared cost-effective in women at the age of 75 and above and at prevalences above 5%. This is because women have higher complication rates during endarterectomy than men, carotid endarterectomy is less effective, and after endarterectomy women still have higher risks for developing a stroke than men[9;10].

Our model has certain limitations. We assumed people eligible for carotid endarterectomy when the severity of the stenosis was 70% or more, whereas the trials we based our estimates of treatment effect on used a severity of 60% or more. We used the 70% cut-off point because the Dutch guidelines recommend

carotid endarterectomy for people with severe carotid artery stenosis of more than 70%[20].

The choice of the 70% cut-off point may have affected our results. Because we used baseline stroke risks for 60% stenosis while supposing treatment from 70% onward this may have resulted in a slightly underestimated long-term risk and subsequent overestimation of the resulting iCERs. After all in individuals with on average higher grades of carotid stenosis, i.e., in accordance with Dutch guideline, the risk of subsequent strokes is somewhat higher, which would likely result in more favourable iCERs. Higher grade stenosis also implies more co-morbidity and higher complication rates resulting in an opposite effect. Probably both effects occur resulting in comparable iCERs had we used a 60% cut-off criteria for CEA.

An overall conclusion previously reported was that a program of screening for asymptomatic carotid artery stenosis to find candidates for endarterectomy costs more per QALY than is usually considered acceptable [2]. These results were sensitive to assumptions about the duration of reduction in the risk for stroke from endarterectomy[2]. We also changed the duration of the reduction of the risk for stroke after endarterectomy. When the duration of the reduction was 3 years, screening was not cost-effective while lifetime effect was very cost-effective. The last will be quite unlikely. At last, after adding non-compliance to screening, endarterectomy or both, screening men with a prevalence of severe ACAS of 3% was not cost-effective.

Our results indicate that one-time screening may be cost-effective particularly in subgroups of men with relatively high prevalence of ACAS. It would be very important to find out which group of people indeed harbours these prevalence rates. Population based studies generally indicate prevalence rates well below the rates required for screening and a subsequent CEA to become cost-effective[18].

In conclusion, one-time screening for ACAS appeared cost-effective in specific subgroups with high prevalence rates. For men above the age of 65 and 75 years the prevalence of severe ACAS has to be over 3%. In 75-year-old women screening appears cost-effective when the prevalence of severe ACAS is at least 5%.

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Chapter 5

Cost-effectiveness of one-time screening for asymptomatic carotid artery stenosis, followed by cardiovascular risk factor management and/or endarterectomy

Abstract

Purpose
Studies on the cost effectiveness of screening for asymptomatic carotid artery stenosis (ACAS) generally assume that carotid endarterectomy (CEA) will be performed once severe stenosis is diagnosed. However, the potential of cardiovascular risk factor management (CVRM) has generally been ignored. This contrasts with current guidelines suggesting that for individuals identified with a moderate (50-69%) and especially severe (>70%) carotid stenosis one should consider CVRM. Thus the present analysis aims to evaluate the cost-effectiveness of screening for ACAS while explicitly taking CVRM into account.

Method
With a Markov model and Monte Carlo simulation hypothetical cohorts of individuals were simulated. The model parameters reflected prevalence distribution according to grade of stenosis (<50%, 50-69% and 70-99%), sex and co-morbidity, and took into account National statistics on survival and stroke occurrence. Costs, effects in terms of stroke and overall survival and utility estimates were literature based. We assumed that CVRM would reduce stroke incidence by 19% in those identified with moderate to severe stenosis, independent of whether or not CEA had been performed. Accounting for patient characteristics (age, sex and co-morbidity) prevalence thresholds for screening to become cost-effective (assuming a societal willingness to pay of €20,000 euro per Quality adjusted life year) were identified. The time horizon used for the analyses was life time, and costs and effects were discounted by 4%.

Results
One-time screening for ACAS appeared cost-effective in a population of 35-year-old men with a prevalence of severe carotid stenosis of at least 5%. In men aged 40 years or above screening was cost-effective for a prevalence of severe carotid stenosis of 0.1% and above. The benefit was essentially driven by CVRM. In a population of 45-year-old women screening was cost-effective when the prevalence of severe carotid stenosis was at least 10%. Screening was cost-effective for a population of women aged 50 years and above with a prevalence of severe stenosis over 0.1%. Again all benefit ensued from CVRM. Overall, cost-effectiveness was determined by CVRM. In fact CEA tended to decrease QALY gain and thus increased the incremental cost-effectiveness ratio.

Conclusion

The benefit of population-based screening for ACAS results from CVRM rather than carotid artery desobstruction. Our findings suggest that compared with no screening population based screening might be cost-effective in men aged 40 years and above and in women screening above the age of 50 with a prevalence of severe carotid stenosis of at least 0.1%, with drugs rendering the benefit.

Introduction

The benefit of carotid endarterectomy for patients with severe asymptomatic carotid artery stenosis (ACAS) has been shown[1;2]. As a consequence, the discussion on screening for ACAS in asymptomatic populations has become opportune. The overall benefit of screening clearly depends on the prevalence of the disease, the sensitivity and specificity of the screening tool, the complication rate of the reference test, the complication rate of the treatment and the benefits of the treatment in terms of event reduction[3;4].

Among individuals with proven carotid stenosis the risk of any stroke or TIA increases with stenosis degree[5]. Further, the risk of any stroke or TIA is generally about 2 to 5.5 times higher among patients with severe (>70%) stenosis compared with patients without stenosis[5]. Importantly, due to the systemic nature of atherosclerosis carotid stenosis also is an indicator of elevated risk of non-stroke vascular events, especially myocardial infarction.

Previous reports suggested that population-based screening among middle-aged and elderly adults may be warranted, yet only in subgroups with a relatively high prevalence of severe ACAS[6-8] (de Weerd et al, submitted). In these studies screening was followed by endarterectomy if the patient had severe stenosis (>70%). However, cardiovascular risk factor management (CVRM) had not been taken into account. This apparent omission may have originated from the separate lines of development, i.e., from a primary surgical as opposed to a medical point of view. Nowadays, CVRM plays an important role in preventing all cause mortality and vascular events[9-11] and thus should be evaluated in integration. The management of significant carotid stenosis will become more drug focused[12] and accordingly the impact of CVRM on the cost-effectiveness of screening for asymptomatic carotid artery stenosis needs to be studied.

The aim of the present analysis was to evaluate the cost-effectiveness of screening for asymptomatic carotid artery stenosis by Duplex followed by CVRM in participants with over 50% stenosis and additional endarterectomy in participants with severe stenosis (>70%).

Method

Model
We developed a Markov model and used Monte Carlo simulation to estimate the long-term effects of screening for carotid artery stenosis with Duplex. The principle of a Markov model is that it defines a number of discrete health states and it assumes that at any point in time a person is in one of these health states. During a specified period of time (time cycle) persons can move from one health state to another as determined by transition probabilities. We defined five health states: healthy, post minor stroke, post major stroke, post myocardial infarction (MI) and death. The model was designed to simulate cohorts of thus far asymptomatic men and women.

Screening arm
For individuals who underwent Duplex ultrasound screening, we considered two thresholds for positive results: >70% stenosis and 50-70% stenosis. If the Duplex ultrasound examination result was indicative of severe stenosis (>=70%, true or false positive), individuals received cardiovascular risk factor management (CVRM). In addition, a computed tomographic angiographic (CTA) examination was performed to confirm the presence of severe stenosis. We assumed that CTA has no complications. If CTA confirmed severe stenosis patients underwent carotid endarterectomy (CEA).
If the Duplex ultrasound examination result was indicative of moderate stenosis (50-70%, true or false positive), individuals received cardiovascular risk factor management (CVRM).

Carotid endarterectomy
Patients who underwent CEA may experience a complication and as a result die during or immediately after the intervention ("death" state), or survive with mild or moderate to severe disability ("minor or major stroke" state), or survive without complications and have normal neurological function ("no event" state). The benefit of carotid endarterectomy was initially assumed to last for five years[13]. The latter was varied in scenario analyses.

Cardiovascular risk factor management
Participants eligible for cardiovascular risk factor management received statins according to the CVRM guidelines[14]. CVRM was assumed to reduce the risks of MI and stroke by 30% and 19%[9], respectively.

No-screening arm

The no-screening arm did not include the initial Duplex screening, and obviously an underlying risk of stroke persisted. Individuals may die from stroke or other causes in the subsequent years or have non-fatal stroke or MI.

Variables

Input parameters, including transition probabilities, treatment effects of CEA and utilities are shown in table 1. This table lists parameters for a 65-year-old man. Because the model cycle is one year, transition probabilities reflect annual incidence rates for the events of interest. Most parameters were derived from literature, see **table 1**. Based on the stroke incidence among patients in the carotid endarterectomy trials[1;2] we assumed that people with severe asymptomatic stenosis had a five times higher risk of stroke compared with people without severe asymptomatic stenosis. Additionally, we assumed that people with moderate stenosis had a two times higher risk[15].

Costs

We conducted our economic analysis from the healthcare payer perspective. Event-related costs in the first year and subsequent years were distinguished because health care costs immediately after an event are higher. The costs of Duplex, CTA, CEA, stroke care during the first year, chronic care during subsequent years, costs for CVRM and the costs of death were extracted from literature [16;17]. All costs estimates were updated to 2008 with the Dutch inflation indices[18] and calculated in Euros.

Analysis

Life-years, QALYs and costs were calculated over a lifetime horizon. Incremental cost-effectiveness ratios (ICERs) were defined as the difference in costs divided by the difference in QALYs. Screening was considered cost-effective up to an incremental cost-effectiveness ratio of 20,000 Euros per QALY gained[19]. All analyses were conducted in hypothetical cohorts of 100,000 men and women aged 35, 40, 45 or 50 years with increasing prevalence of severe asymptomatic carotid stenosis (0.1%, 1%, 3%, 5%, 10%, 15%, 20%, 25% and 30%). The prevalence of moderate stenosis (50-70%) is a function of the prevalence of severe stenosis. The prevalence of severe stenosis was multiplied by 1.41[20] for the prevalence of moderate stenosis. The costs and benefits were both discounted by four percent. Sensitivity analyses were performed to evaluate the effect of varying the input parameters over the ranges given in **Table 1**.

Additionally, we evaluated the following scenarios: 1) costs were discounted at 4% and benefits at 1.5% in accordance with current Dutch guidelines[21] 2) costs and benefits were not discounted 3) correction for the competing mortality and morbidity in men and women with severe asymptomatic carotid artery stenosis by doubling the death risks 4) changing the 5 year benefit of endarterectomy into 3 year benefit 5) introducing non-compliance with screening (20%) 6) introducing non-compliance with endarterectomy (20%), 7) introducing non-compliance with screening and endarterectomy (20%) 8) introducing non compliance with CVRM (20%)[22] and 9) analysis of the effects of CVRM alone i.e., individuals with moderate and severe stenosis all were prescribed CVRM only.

To assess the uncertainty regarding the modelled output, we performed probabilistic sensitivity analyses with Monte Carlo simulation. We evaluated the clinical courses of 100,000 hypothetical people for both strategies (screening versus no screening) 200 times, with each simulation involving a random draw from each of the input parameter distributions given in **Table 1**. Multiple outputs were thus calculated[19].

Table 1; Incidence, case fatality, and overall mortality rates for a 65-year-old person and effectiveness of endarterectomy and statin treatment, utilities, costs and their 95% confidence intervals.

Parameters	*Men*	*Women*	*Distribution*	*Reference*
Overall one year mortality rate				
(per 100,000 person years)	1994 (1899-2089)	1010 (945-1075)		18
Stroke				
Incidence general population				
(per 100,000 person years)	551 (524-579)	339 (319-360)	Beta	25
Incidence severe stenotic population				
(per 100,000 person years)	2122 (2016-2227)	1306 (1227-1386)	Beta	25
Case fatality stroke (%)	24 (22-26)	26 (23-29)	Beta	25
Relative risk of stroke in severe stenotic population	5.0 (4.0-6.0)	5.0 (4.0-6.0)	Log linear	1;2
Relative risk of stroke in moderate stenotic population	2.0 (1.0-3.0)	2.0 (1.0-3.0)	Log linear	15
Screening				
Sensitivity Duplex Ultrasound (≥50% stenosis)	86 (76-95)	86 (76-95)	Triangular	16
Specificity Duplex Ultrasound (≥50% stenosis)	87 (84-90)	87 (84-90)	Triangular	16
Sensitivity Duplex Ultrasound (≥70% stenosis)	86 (84-89)	86 (84-89)	Triangular	23
Specificity Duplex Ultrasound (≥70% stenosis)	87 (84-90)	87 (84-90)	Triangular	23
Intervention risks				
Perioperative strokes after CEA	0.009 (0.006-0.019)	0.019 (0.011-0.030)	Beta	1;2
Perioperative mortality after CEA	0.005 (0.002-0.009)	0.009 (0.005-0.019)	Beta	1;2
Intervention benefits				
Relative risk of stroke after CEA	0.37 (0.27-0.50)	0.51 (0.33-0.79)	Log linear	1;2
Relative risk of stroke after statin therapy	0.81 (0.68-0.88)	0.81 (0.68-0.88)	Log lineair	9
Relative risk of MI after statin therapy	0.70 (0.61-0.81)	0.70 (0.61-0.81)	Log lineair	9
Utilities				
Stroke	0.62 (0.60-0.78)	0.62 (0.60-0.78)	Beta	26
Myocardial Infarction	0.88 (0.80-0.95)	0.88 (0.80-0.95)	Beta	27
Taking CVRM	1.0 (0.99-1.0)	1.0 (0.99-1.0)	Beta	28
Costs				
Doppler Ultrasonography	60			16
CTA	290			17
Carotid endarterectomy	3457			16
Chronic care for minor stroke during 1st year	6383			16
Chronic care for minor stroke during subsequent years	1092			16
Chronic care for major stroke during 1st year	36400			16
Chronic care for major stroke during subsequent years	21254			16
Chronic care for MI during 1st year	15330			29
Chronic care for MI during subsequent years	996			30
Death	2715			16
Cardiovascular risk management	95			21;31;32

Results

Health outcomes

The number of events for a hypothetical cohort of 100,000 men and women aged 35, 40 and 45 years and of 50 year old women with increasing prevalence of severe carotid artery stenosis in both the screening arm and no-screening arm are presented in **Tables 2 and 3**. Screening resulted in health benefits in men of all ages. In 35-year-old men this benefit ranged from 0.02 QALY when the prevalence of severe ACAS was 0.1% to 0.13 QALY when the prevalence was 30%. In 45-year-old men health benefits ranged from 0.03 QALY to 0.19 QALY **(Table 2)**.

In women screening also resulted in QALY gain in all ages. This QALY gain ranged from 0.01 QALY when the prevalence of severe ACAS was 0.1% to 0.04 QALY when the prevalence was 30%, in women aged 35 year. In women aged 45-year-old women health benefits ranged from 0.02 QALY to 0.10 QALY **(Table 3)**.

Cost and incremental cost-utility ratios

Mean life-time costs of screening for a 35-year-old man ranged from 4,500 euros to 9,005 euros. The incremental cost effectiveness ratio (iCER) thus ranged from 24,000 euros when the prevalence of severe ACAS was 0.1% to 12,200 euros when the prevalence of severe ACAS was 30%. Accordingly, with a cut-off point of 20,000 euros screening was cost-effective in men aged 35 year-old men with a prevalence of severe carotid stenosis of at least 3%. In 40 and 45 year old men screening was cost- effective when the prevalence of carotid artery stenosis was at least 0.1% **(Table 2)**.

For women mean life-time costs of screening at the age of 35 year ranged from 3,600 euros when the prevalence of severe ACAS was 0.1% to 8,400 euros when the prevalence of severe ACAS was 30%. The iCER ranged from 47,300 euros per QALY gained when the prevalence of severe ACAS was 0.1% to 54,500 euros per QALY gained when the prevalence of severe ACAS was 30%. In 45-year-old women the iCER ranged from 25,000 euros per QALY gained when the prevalence of severe ACAS was 0.1% to 16,100 euros per QALY gained when the prevalence of severe ACAS was 30%. Thus in 35 and 40 year-old women screening was not cost-effective. When the prevalence of severe ACAS was 10% or more in 45 year old women screening became cost-effective. In 50 year old women screening became cost-effective with the prevalence of severe ACAS surpassing 0.1% **(Table 3)**.

Table 2: Quality adjusted life expectancy and costs of screening versus no screening on cohorts of Dutch men of different ages and with different prevalences of severe ACAS over a life-time period.

Age (yrs.)	Prev.	Percentage Major Stroke No Screening	Screening	Difference	Percentage Minor Stroke No Screening	Screening	Difference	QALY Screening	No Screening	Difference	Costs Screening	No Screening	Difference	iCER
35	0.1%	4.7%	4.5%	0.2%	9.4%	9.0%	0.4%	19.525	19.506	0.019	4467	4006	461	24135
	1.0%	4.9%	4.7%	0.2%	9.7%	9.3%	0.4%	19.518	19.496	0.022	4604	4110	493	22116
	3.0%	5.2%	5.0%	0.2%	10.4%	9.9%	0.5%	19.502	19.472	0.029	4907	4343	564	19199
	5.0%	5.6%	5.3%	0.3%	11.1%	10.6%	0.6%	19.486	19.449	0.036	5211	4575	635	17417
	10.0%	6.4%	6.1%	0.4%	12.9%	12.1%	0.8%	19.446	19.391	0.054	5970	5156	813	15002
	15.0%	7.3%	6.8%	0.5%	14.7%	13.7%	1.0%	19.405	19.333	0.072	6729	5737	991	13778
	20.0%	8.2%	7.6%	0.6%	16.4%	15.2%	1.2%	19.365	19.275	0.090	7488	6318	1169	13037
	25.0%	9.1%	8.4%	0.7%	18.2%	16.8%	1.4%	19.325	19.217	0.107	8247	6899	1347	12542
	30.0%	10.0%	9.2%	0.8%	19.9%	18.3%	1.6%	19.285	19.160	0.125	9005	7480	1525	12186
40	0.1%	5.0%	4.8%	0.2%	10.0%	9.6%	0.4%	18.426	18.403	0.024	5003	4578	425	18049
	1.0%	5.2%	5.0%	0.2%	10.3%	9.9%	0.4%	18.418	18.390	0.028	5143	4693	450	16276
	3.0%	5.5%	5.3%	0.2%	11.0%	10.5%	0.5%	18.400	18.363	0.037	5454	4947	507	13758
	5.0%	5.9%	5.6%	0.3%	11.7%	11.2%	0.6%	18.381	18.335	0.046	5764	5201	563	12244
	10.0%	6.8%	6.4%	0.4%	13.5%	12.7%	0.8%	18.335	18.266	0.069	6541	5837	704	10221
	15.0%	7.6%	7.2%	0.5%	15.3%	14.3%	1.0%	18.289	18.198	0.092	7318	6473	845	9208
	20.0%	8.5%	7.9%	0.6%	17.0%	15.9%	1.2%	18.243	18.129	0.115	8095	7109	987	8599
	25.0%	9.4%	8.7%	0.7%	18.8%	17.5%	1.3%	18.198	18.060	0.138	8872	7744	1128	8193
	30.0%	10.3%	9.5%	0.8%	20.6%	19.0%	1.5%	18.152	17.991	0.161	9649	8380	1269	7903
45	0.1%	5.1%	4.9%	0.2%	10.1%	9.7%	0.4%	17.123	17.096	0.027	5432	5045	387	14267
	1.0%	5.2%	5.0%	0.2%	10.4%	10.0%	0.4%	17.114	17.082	0.032	5573	5167	406	12683
	3.0%	5.6%	5.3%	0.2%	11.1%	10.6%	0.5%	17.094	17.051	0.043	5887	5437	450	10461
	5.0%	5.9%	5.6%	0.3%	11.8%	11.3%	0.6%	17.073	17.019	0.054	6201	5708	493	9141
	10.0%	6.8%	6.4%	0.4%	13.6%	12.8%	0.8%	17.023	16.941	0.081	6985	6384	601	7397
	15.0%	7.7%	7.2%	0.5%	15.4%	14.4%	1.0%	16.972	16.863	0.109	7770	7061	709	6531
	20.0%	8.6%	8.0%	0.6%	17.1%	16.0%	1.2%	16.921	16.785	0.136	8555	7737	818	6013
	25.0%	9.4%	8.8%	0.7%	18.9%	17.5%	1.4%	16.871	16.707	0.163	9340	8414	926	5669
	30.0%	10.3%	9.5%	0.8%	20.6%	19.1%	1.6%	16.820	16.629	0.191	10124	9090	1034	5423

Table 3: Quality adjusted life expectancy and costs of screening versus no screening on cohorts of Dutch women of different ages and with different prevalences of severe ACAS over a life-time period.

Table 3: Quality adjusted life expectancy and costs of screening versus no screening on cohorts of Dutch women of different ages and with different prevalences of severe ACAS over a life-time period.

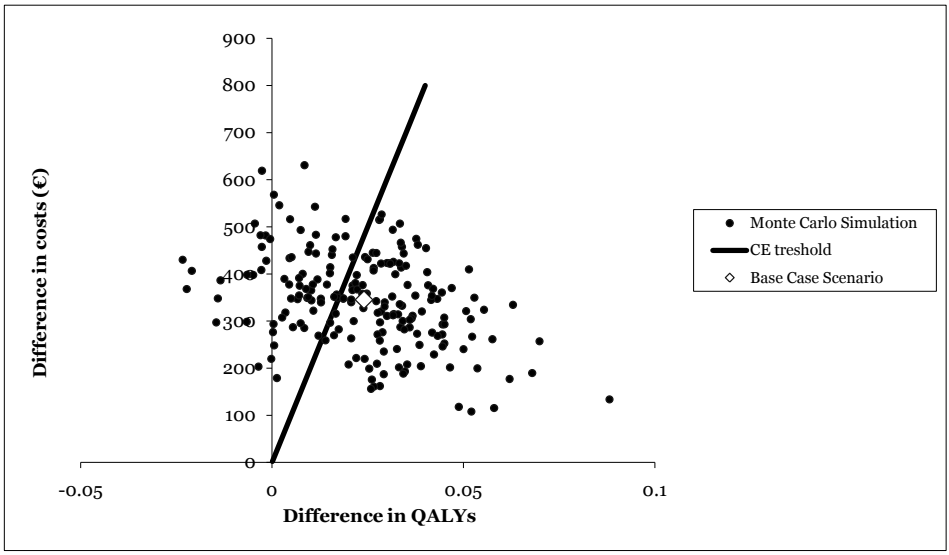
		Percentage Major Stroke			Percentage Minor Stroke			QALY			Costs			
Age (yrs.)	**Prev.**	**No Screening**	**Screening**	**Difference**	**No Screening**	**Screening**	**Difference**	**Screening**	**No Screening**	**Difference**	**Screening**	**No Screening**	**Difference**	**iCER**
35	0.1%	4.9%	4.7%	0.2%	9.8%	9.4%	0.4%	20.469	20.458	0.011	3532	3021	510	47262
	1.0%	5.1%	4.8%	0.2%	10.2%	9.7%	0.5%	20.460	20.449	0.012	3680	3122	557	47975
	3.0%	5.5%	5.2%	0.3%	10.9%	10.3%	0.6%	20.441	20.427	0.013	4009	3347	662	49248
	5.0%	5.8%	5.5%	0.3%	11.7%	11.0%	0.7%	20.421	20.406	0.015	4337	3571	766	50217
	10.0%	6.8%	6.3%	0.5%	13.6%	12.6%	1.0%	20.372	20.352	0.020	5160	4132	1027	51861
	15.0%	7.7%	7.1%	0.6%	15.5%	14.2%	1.2%	20.322	20.298	0.024	5982	4693	1288	52891
	20.0%	8.7%	7.9%	0.8%	17.4%	15.8%	1.5%	20.273	20.244	0.029	6804	5255	1549	53596
	25.0%	9.6%	8.7%	0.9%	19.2%	17.5%	1.8%	20.224	20.190	0.033	7626	5816	1810	54110
	30.0%	10.6%	9.5%	1.0%	21.1%	19.1%	2.1%	20.175	20.137	0.038	8448	6377	2071	54501
40	0.1%	5.8%	5.6%	0.2%	11.6%	11.1%	0.5%	19.645	19.630	0.015	4014	3532	483	32806
	1.0%	6.0%	5.7%	0.3%	11.9%	11.4%	0.5%	19.634	19.618	0.016	4166	3643	523	31821
	3.0%	6.4%	6.1%	0.3%	12.7%	12.1%	0.6%	19.611	19.591	0.020	4504	3890	614	30236
	5.0%	6.8%	6.4%	0.4%	13.5%	12.8%	0.7%	19.588	19.563	0.024	4841	4136	705	29158
	10.0%	7.8%	7.3%	0.5%	15.5%	14.6%	1.0%	19.529	19.495	0.034	5685	4753	932	27540
	15.0%	8.8%	8.1%	0.6%	17.5%	16.3%	1.2%	19.471	19.427	0.044	6528	5369	1159	26640
	20.0%	9.8%	9.0%	0.7%	19.5%	18.0%	1.5%	19.412	19.359	0.053	7372	5986	1386	26068
	25.0%	10.7%	9.9%	0.9%	21.5%	19.8%	1.7%	19.354	19.291	0.063	8216	6603	1613	25672
	30.0%	11.7%	10.8%	1.0%	23.5%	21.5%	2.0%	19.295	19.223	0.072	9059	7219	1840	25381
45	0.1%	6.1%	5.8%	0.2%	12.2%	11.7%	0.5%	18.598	18.580	0.018	4373	3920	453	25014
	1.0%	6.3%	6.0%	0.3%	12.5%	12.0%	0.5%	18.586	18.566	0.021	4525	4037	488	23673
	3.0%	6.7%	6.3%	0.3%	13.3%	12.7%	0.6%	18.560	18.534	0.026	4864	4297	567	21618
	5.0%	7.1%	6.7%	0.4%	14.1%	13.4%	0.7%	18.534	18.502	0.032	5202	4556	646	20287
	10.0%	8.0%	7.6%	0.5%	16.1%	15.1%	1.0%	18.468	18.423	0.046	6048	5205	844	18385
	15.0%	9.0%	8.4%	0.6%	18.1%	16.9%	1.2%	18.403	18.343	0.060	6894	5853	1041	17374
	20.0%	10.0%	9.3%	0.7%	20.1%	18.6%	1.4%	18.338	18.264	0.074	7740	6502	1238	16747
	25.0%	11.0%	10.2%	0.8%	22.0%	20.4%	1.7%	18.272	18.184	0.088	8586	7150	1436	16320
	30.0%	12.0%	11.1%	1.0%	24.0%	22.1%	1.9%	18.207	18.105	0.102	9432	7799	1633	16010

50	0.1%	6.1%	5.9%	0.2%	12.2%	11.7%	0.5%	17.357	17.336	0.021	4664	4245	419	19942
	1.0%	6.3%	6.0%	0.3%	12.6%	12.0%	0.5%	17.344	17.320	0.024	4815	4365	450	18507
	3.0%	6.7%	6.4%	0.3%	13.4%	12.7%	0.6%	17.316	17.284	0.032	5151	4633	518	16385
	5.0%	7.1%	6.7%	0.4%	14.1%	13.4%	0.7%	17.287	17.249	0.039	5487	4901	585	15057
	10.0%	8.1%	7.6%	0.5%	16.1%	15.2%	1.0%	17.216	17.159	0.057	6326	5571	755	13221
	15.0%	9.1%	8.5%	0.6%	18.1%	16.9%	1.2%	17.145	17.070	0.075	7165	6241	924	12273
	20.0%	10.0%	9.3%	0.7%	20.1%	18.6%	1.4%	17.075	16.981	0.093	8005	6911	1093	11694
	25.0%	11.0%	10.2%	0.8%	22.1%	20.4%	1.7%	17.004	16.892	0.112	8844	7581	1263	11304
	30.0%	12.0%	11.1%	1.0%	24.0%	22.1%	1.9%	16.933	16.803	0.130	9683	8251	1432	11023

Sensitivity analyses

Sensitivity and scenario-analyses were performed in 35-year-old men with a prevalence of severe ACAS of 3%. Uncertainty regarding the likelihood of suffering a minor or major stroke contributed most to the costs of screening together with uncertainty regarding the likelihood of having a complication during carotid endarterectomy. Uncertainty regarding the utility score after a minor or major stroke and the utility score while on CVRM every day had the highest impact on the health benefits of screening. Sensitivity analysis also showed that even though the point estimate of a 35-year-old cohort of men with a prevalence of ACAS of 3% indicated that screening would be cost-effective, there would still be a 25% chance that screening resulted in QALY loss (dots on the left of the y-as) **(Figure 1)**.

Figure 1. Monte Carlo simulation results for a hypothetical cohort 35 year-old men with a prevalence of severe ACAS of 5%, plotted on a cost-effectiveness-plane.



The results of the scenario-analyses are presented in **Table 4**. In our base-case scenario screening 35 year-old men with a prevalence of severe ACAS of 3% increased mean QALYs (19.502 vs. 19.472) at a higher cost (4,907 vs. 4,343). The cost per additional QALY was approximately € 19,000. At 1.5% discount rate for benefits and 4% for costs the iCER decreased to 7,938 euro per QALY. Not discounting resulted in an iCER of 6,028 euros per QALY. Correcting for competing mortality and morbidity did not change incremental costs but the difference in

QALY decreased resulting in an iCER of 20,600 euro per QALY gained. When we changed the 5 year annual risk reduction by carotid endarterectomy into 3 year benefit, there was only a small increase in costs. The resulting iCER was 19,700 euro per QALY gained. When we added non-compliance to screening the iCER became higher than the iCER in the base-case scenario, but after adding non-compliance to endarterectomy alone the iCER decreased from the one in the base-case scenario. Adding non-compliance to CVRM resulted in an increased iCER of 26,200 euro per QALY. When we analysed the effects of cardiovascular risk management only, the difference in QALY was somewhat higher than in the base-case scenario and also the costs were lower. Apparently, screening according to this scenario is more cost-effective and in fact dominates the base-case scenario with an iCER of 13,000 euro per QALY compared with no screening **(Table 4)**.

Table 4; Scenario-analyses examining incremental cost-effectiveness ratio in a hypothetical cohort of 35-year-old men with a pevalence of severe ACAS of 3%

	Difference in QALY	Difference in Costs	iCER
Base Case Scenario	*0.029*	*564*	*19199*
Discounting effect 1.5% and costs with 4%	0.071	564	7938
No discounting	0.125	754	6028
Competing Morality and morbidity	0.027	565	20596
3 year effect of endarterectomy	0.029	570	19718
Non compliance screening	0.024	463	19710
Non compliance endarterectomy	0.030	543	18138
Non compliance screening and endarterectomy	0.024	447	18638
Non compliance to CVRM	0.023	597	26206
Excluding endarterectomy	0.032	415	12902

Discussion

Screening followed by endarterectomy and/or CVRM was cost-effective at any prevalence of severe stenosis in men aged over 40 years. In 35-year-old men screening was cost-effective when the prevalence of severe ACAS was at least 5%. Screening was cost-effective in 50-year-old women at a prevalence of at least 1% and in 45-year-old women at a prevalence of severe ACAS of at least 10%.
This difference between men and women can be explained by a lower stroke risk in women in general. Screening in patients with lower risks of course is less efficient than in patients with higher risks. Screening women yields a smaller QALY increase at higher costs.
Based on the results of ACAS, i.e., CEA upon detection of severe asymptomatic stenosis and no CVRM[1], one-time screening was reported to become cost-effective in men but only at high prevalence of severe carotid artery stenosis[6;7]. However, it seems quite unlikely that a subgroups with such high prevalence of severe asymptomatic carotid artery stenosis[6-8] can be easily identified. Moreover, in previous cost-effectiveness studies conventional carotid angiography was used to confirm the positive test result of the Duplex examination[6-8]. However, angiography may not be current practice anymore in many clinics. It is more expensive and carries an inherent risk of complications[23]. We already performed a cost-effectiveness analysis in which Duplex ultrasound was used as screening tool and CTA to confirm the severity of stenosis. The input parameters in this study were extracted from ACAS and ACST[1;2]. One-time screening for severe asymptomatic carotid artery stenosis in the general population appeared cost-effective in 65-year-old men with a prevalence of severe ACAS of at least 3%. In 75-year-old women screening was cost-effective when the prevalence of severe ACAS was at least 5%. In 55- and 65-year old women, screening was not cost-effective (de Weerd et al. submitted). Overall screening and subsequent CEA did not appear cost-effective. However, as in previous reports cardiovascular risk factor management was not accounted for. As such this enhanced comparability, yet, management of significant carotid stenosis likely will become increasingly drug focused[12]. Clearly CVRM should currently be taken into account while balancing the costs and effect of screening. Additionally, we analysed whether screening was cost-effective, when participants with a stenosis of 70% or more did not receive endarterectomy but CVRM only. Without the costs and the benefits of endarterectomy one-time screening with CVRM only remained cost-effective. In other words, endarterectomy might not even be worthwhile in general for those patients. In fact we showed that CVRM only as compared with CVRM and CEA in patients with severe stenosis yields more health gain at lower costs and thus is the dominant scenario. Screening is in effect used to find the

patients who are eligible for CVRM. This would appear to lead to a subsequent question regarding the optimal strategy to identify individuals at increased risk of CVD. Notably, cardiovascular risk factor management not only reduces incident strokes but at the same time protects all other organs from atherosclerotic and other degenerative disease processes[5].

Our model has certain limitations. We assumed people eligible for carotid endarterectomy when the severity of the stenosis was 70% or more, whereas the trials used a severity of 60% or more. We used this cut-off point because the Dutch guidelines recommend carotid endarterectomy for people with severe symptomatic carotid artery stenosis of more than 70%[24]. Because we used baseline stroke risks for 60% stenosis while supposing treatment from 70% onward this may have resulted in a slightly underestimated long-term risk and subsequent overestimation of the pertaining iCERs. Higher grade stenosis also implies more co-morbidity and higher complication rates resulting in an opposite effect. Probably both effects occur resulting in comparable iCERs had we used the 60% stenosis cut-off criterion for CEA.

In addition, we assumed that all patients eligible for endarterectomy and CVRM did actually receive treatment. We do not know for sure whether these patients agree to undergo surgery or take medication correctly. This gives rise to extra costs and no benefits, which renders screening less cost-effective. To try and account for this potential limitation we have performed additional scenario-analyses in which we assessed the effect of non-compliance to screening, carotid endarterectomy and medication use.

Non-compliance with CVRM had a major impact on the iCER. This may be explained by the fact that patients who receive medical therapy need to take them continuously and the effects are also lifelong. When non-compliance increases the cost-effectiveness will be influenced to a great extent. As stated above, we estimated the cost-effectiveness of screening, with CVRM being statins. Additionally we performed a scenario-analysis in which we analyzed the effect of cardiovascular risk management only. In this analysis the QALY gain was even higher than the QALY gain in the base case scenario. This is explained by the complications caused by endarterectomy. Because people may also be prescribed additional blood pressure lowering medication this will influence the cost-effectiveness. The initial costs will be marginally higher but because the effects will also be higher the iCER will remain less than 20,000 euro per QALY. Nevertheless, we did not take into account the effect of CVRM on major other cardiovascular events[9]. Whether population based screening for carotid artery stenosis would indeed appear cost-effective when compared with other methods such as serum cholesterol measurements should be assessed prior to actual implementation.

Finally, we did not take into account the costs incurred for inviting people to a screening service. This indicates slightly higher costs and thus worse iCERs. However, we also did not take into account the effect of CVRM on major other cardiovascular events[9], which would result in lower iCERs.
In conclusion the benefit of population-based screening for ACAS results from CVRM rather than carotid artery desobstruction. Our findings suggest that compared with no screening population based screening might be cost-effective in men aged 40 years and above and in women screening above the age of 50 with a prevalence of severe carotid stenosis of at least 0.1%, with drugs rendering the benefit.

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Chapter 6

Prediction of asymptomatic carotid artery stenosis in the general population: identification of high risk groups

Abstract

Background
Because of a low prevalence of severe carotid stenosis in the general population screening for asymptomatic carotid artery stenosis (ACAS) is not warranted. Possibly, for certain subgroups screening is worthwhile, e.g those with a prevalence of ACAS of 3%. The challenge thus lies in identifying individuals for whom screening might be cost-effective. The present study aims to develop prediction rules for the presence of moderate (>50%) and severe (>70%) ACAS.

Methods
Individual participant records (n=23,706) from four population-based studies were used, i.e., The Tromsø Study, the Malmö Diet and Cancer Study (MDCS), the Carotid Atherosclerosis Progression Study (CAPS) and the Cardiovascular Health Study (CHS). Individuals with prior symptoms of carotid artery stenosis were not part of the original cohorts. We constructed prediction models to estimate the probability of moderate (>50%) and severe (>70%) ACAS from participant characteristics with multivariate logistic regression analysis. We assessed the calibration and discrimination of the models and used bootstrapping to correct for overfitting.

Results
Presence of moderate (>50%) ACAS was related to age, sex, HDL cholesterol, LDL cholesterol, triglycerides, systolic and diastolic blood pressure, body mass index, waist-to-hip-ratio and smoking. The area under the receiver operating characteristic curve (AUC) of the prediction model for moderate (>50%) ACAS was 0.82 (95% CI 0.78-0.83). Among participants with a very low absolute risk (92% of the population) the probability of moderate (>50%) stenosis being present was 1.3%. In those with a high absolute risk (0.8% of the population) the probability of moderate (>50%) stenosis being present was 16.4%.
Severe (>70%) ACAS was related to age, sex, HDL cholesterol, systolic and diastolic blood pressure, and smoking. The AUC was 0.79 (0.76-0.83). Among participants with a low absolute risk (66% of the population) the probability of severe (>70%) stenosis being present was 0.1% and in participants with a high absolute risk (7% of the population) the probability of severe (>70%) stenosis being present was 3.4%.

Conclusions

We developed a clinical prediction rule that allows identification of subgroups with relatively high prevalence of severe (>70%) ACAS. When population screening for ACAS is considered, use of the prediction rule is suggested to identify subgroups in order to substantially reduce the number needed to screen.

Introduction

Stroke is the leading cause of hospitalization and death in both men and women in nearly all European countries and the third major cause of death in the United States[1;2]. Clearly, stroke is a major source of morbidity and long-term disability, and poses a substantial economic burden in terms of health care and societal costs worldwide[3]. Studies have reported an annual risk for stroke of approximately 2-5% for patients with severe (>70%) asymptomatic artery carotid stenosis [4-7]. Further studies have shown the benefits of carotid endarterectomy (CEA) in patients with severe (>70%) symptomatic[8;9] and asymptomatic carotid artery stenosis[10;11]. This, however, is insufficient to plan and implement (cost-) effective screening for and treatment of populations at (high) risk of severe (>70%) asymptomatic carotid stenosis.

Duplex ultrasound screening for ACAS in the general population appeared cost-effective in 65-year-old men with a prevalence of severe (>70%) ACAS above 3% (M. de Weerd, Submitted). In 75-year-old women screening appeared cost-effective with a prevalence of severe (>70%) ACAS above 5% (M.de Weerd, Submitted). Prior studies suggested that screening could become cost-effective at a prevalence of ACAS of at least 20%[12-14]. These results corroborate the notion that in case of a relatively high prevalence of severe (>70%) ACAS and sufficiently long life expectancy screening for ACAS is warranted. Presently, such subgroups can not be accurately identified.

The present study aims at developing a prediction rule for identification of individuals with a high probability of having a moderate (>50%) or severe (>70%) asymptomatic carotid artery stenosis in the general population.

Methods

Study population

We used individual participant data from four observational studies in the general population on cardiovascular diseases; The Tromsø Study, the Malmö Diet and Cancer Study (MDCS), the Carotid Atherosclerosis Progression Study (CAPS) and the Cardiovascular Health Study (CHS). All studies obtained extensive information on degree of stenosis and potential determinants thereof. Thus, the prevalence of ACAS may be established accurately and predictors of ACAS were evaluated. The individual studies were previously detailed elsewhere[18-22]. In brief, the *Tromsø Study* is a population-based prospective study in Tromsø, Norway. People aged 55 to 74 years eligible for ultrasound examination were invited, in total 6,727 participants (attendance rate 77%) were screened and informed consent was obtained from 6,659 participants[15]. In the population-based *Malmö Diet and Cancer Study (MDCS)* a total of 30,587 participants attended (attendance rate 71.2%) between 1974 and 1992. A random sample of 6,103 (20%) participants had an ultrasound examination[16;17]. In the *Carotid Atherosclerosis Progression Study* (CAPS), members of a German primary healthcare scheme were invited of whom 6,962 (attendance rate 21%) agreed to take part[18]. The *Cardiovascular Health Study* is a community-based, prospective study of people aged ≥65 years including 5,888 participants (attendance rate 57%)[19].

Baseline characteristics

The following baseline characteristics were recorded in each study: age, sex, race, family history on kidney disease, coronary artery disease, and diabetes mellitus, highest education level, income, history of coronary and/or cerebrovascular disease and information on medication use. In addition, data on blood pressure, diabetes mellitus, hypercholesterolemia, current smoking, waist-to-hip ratio (WHR) and body mass index (BMI) were recorded.

Outcomes

Moderate (>50%) ACAS was defined as ≥50% stenosis and severe (>70%) ACAS as ≥70% stenosis, measured by Doppler ultrasonography supported by B-mode ultrasound imaging in three of the four studies[20]. When both carotid arteries were measured, we used the most severe stenosis grade observed.

Model development

All missing values were imputed with single regression techniques using information from all individuals without missing values on that variable, since

deleting subjects with missing values often leads to biased findings and to a loss of statistical power[21]. The grade of stenosis was missing in 0.2% of the participants, predictors were missing for 0.1% to 5.2% of the participants. Restricted cubic spline functions and graphs were used to determine whether continuous variables could be analyzed as linear terms or required a transformation[22;23]. All candidate predictors were included in a logistic model and were step by step excluded using the likelihood ratio test with a p-value above 0.50[23;24].

Model performance

To study the performance of the final prediction model, we assessed its discrimination and calibration. Discrimination is the ability of the model to distinguish between participants with moderate (>50%) or severe (>70%) stenosis and participants without moderate (>50%) or severe (>70%) stenosis, and is quantified as the area under the receiver operating characteristic curve (AUC). An AUC ranges from 0.5 (no discrimination) to 1 (perfect discrimination). Calibration refers to the agreement between the predicted probabilities and observed frequencies of stenosis degree, which was tested with the Hosmer-Lemeshow statistic [25].

Model validation

Prediction models derived with multivariable regression analysis are known for overestimated regression coefficients. This results in too extreme predictions when applied in new participants[22;26]. Therefore, we validated our model internally with bootstrapping techniques where in each bootstrap sample the entire modeling process was repeated. This resulted in a shrinkage factor for the regression coeffecients[22;27]. The bootstrap procedure was also used to estimate the AUC corrected for over optimism. The corrected AUC may be considered as an estimate of discriminative ability expected in future similar participants.

Clinical application

The final model was transformed into a clinical prediction rule to facilitate practical application of the model. The absolute risks per participant were calculated using the prediction rules; participants were classified in very low (≤5.0%), low (5.0-10.0%), moderate (10.0-15.0%) and high (≥15.0%) predicted probability of having moderate stenosis and very low (≤0.5%), low (0.5 to 1.0%), moderate (1.0-2.0%) and high (≥2.0%) probability of having severe stenosis. Sensitivity, specificity, positive and negative predicted values were calculated for the same cut-off values. Data were analyzed using SPSS for Windows (version 15.0, SPSS Inc., Chicago, Illinois, USA) and R (version 2.4.0, http://www.r-project.org/).

Results

Participant population

General characteristics of the study population are presented in **table 1**. The mean age was 61 ± 12 years and 46% of the participants were men. Mean LDL cholesterol was 3.6 ±1.0 mmol/l, mean HDL cholesterol was 1.46 ± 0.4 mmol/l, mean diastolic blood pressure was 80.1 ± 12.8 mmHg and mean systolic blood pressure was 141.2 ± 21.5 mmHg. The proportion of participants that smoked was 23%. The overall prevalence of moderate (>50%) stenosis was 2.0% and the prevalence of severe (>70%) stenosis was 0.5%.

Table1. General characteristics of the study population, by center.

	Tromsø	MDCS	CAPS	CHS	Total
Nr. of participants	6659	6103	5056	5888	23706
Mean age, y *(sd)*	60.2 *(10.1)*	57.5 *(5.9)*	50 *(13.1)*	72.8 *(5.6)*	60.5 (12.1)
Male sex, n (%)	3298 (49.5)	2572 (42.1)	2471 (48.9)	2495 (42.4)	10836 (45.7)
History of disease, n (%)					
Coronary heart disease	822 (12.3)	102 (1.7)	108 (2.1)	1154 (19.6)	2186 (9.2)
Cerebrovascular disease*	182 (2.7)	69 (1.2)	52 (1.0)	349 (5.9)	652 (2.8)
Body Mass Index mean kg/m2 *(sd)*	26.1 *(3.9)*	25.9 *(4.0)*	26.6 *(4.1)*	26.7 *(4.7)*	26.3 (4.2)
Waist-Hip Ratio, mean *(sd)*	0.87 *(0.08)*	0.85 *(0.09)*	0.95 *(0.11)*	0.93 *(0.09)*	0.9 (0.1)
Mean systolic BP *(sd)*	145 *(22.5)*	141 *(19)*	127 *(17.0)*	136.5 *(21.8)*	141.2 *(21.5)*
Mean Diastolic BP, *(sd)*	83 *(12)*	87 *(9.5)*	77.3 *(10.1)*	70.7 *(11.4)*	79.9 *(12.8)*
Diabetes, n (%)	217 *(3.3)*	157 *(2.6)*	134 *(2.7)*	722 *(12.3)*	1230 *(5.2)*
Smoker, n (%)	2116 (31.8)	1618 (28.1)	1055 (20.9)	700 (11.9)	5489 (23.2)
Lipids, mean *(sd)*					
Total Cholesterol	6.75 *(1.29)*	6.2 *(1.1)*	NR	5.4 *(1.1)*	6.1 *(1.3)*
HDL Cholesterol	1.5 *(0.43)*	1.4 *(0.4)*	1.54 *(0.44)*	1.37 *(0.37)*	1.46 *(0.42)*
LDL Cholesterol	NR	1.4 *(0.8)*	3.35 *(0.93)*	4.16 *(0.98)*	3.6 *(1.02)*
Triglycerides	1.7 *(1.1)*	4.2 *(0.9)*	1.5 *(0.99)*	1.37 *(0.8)*	1.55 *(0.95)*
Methods of measure stenosis					
Duplex Ultrasonography	yes	yes	yes	no	
-Lumen diameter method	yes	yes	no	.	
-Cross sectional lumen method	yes	no	yes	.	
Outcomes					
Moderate (>50%) stenosis, n (%)	121 (1.8)	39 (0.6)	40 (0.8)	266 (4.5)	466 (2.0)
Severe (>70%) stenosis, n (%)	48 (0.7)	5 (0.1)	9 (0.2)	65 (1.1)	127 (0.5)

*=participants with a cerebrovascular disease more than 6 months before baseline-date, MDCS = Malmö Diet and Cancer Study, CAPS = Carotid Atherosclerosis Progression Study, CHS =Cardiovascular Health Study, HDL = high density lipoprotein, LDL = low density lipoprotein

Model development and performance moderate (>50%) stenosis

In the multivariable regression analysis, age, sex, HDL cholesterol, LDL cholesterol, triglycerides, systolic and diastolic blood pressure, BMI, WHR and smoking emerged as independent predictors (**Table 2A**). The calibration of the model was good, confirmed by a non-significant Hosmer and Lemeshow test (P=0.10). The AUC of the model after correction for over optimism was 0.82 (95% CI, 0.78 to 0.83). Bootstrapping yielded a shrinkage factor of 0.98 for the moderate (>50%) stenosis model.

Clinical application moderate (>50%) stenosis

In the very low risk group (n=21,676), the prevalence of moderate (>50%) stenosis was 1.3%. In the high risk group (n=207) the prevalence of moderate (>50%) stenosis was 16.4% (table 3). Using an absolute risk threshold of ≥10% (moderate risk) would mean that 2.3% (542 out of 23,706) of the population would be identified at risk for moderate (>50%) stenosis in whom 70 (12.9%) would ultimately diagnosed with moderate (>50%) stenosis. Conversely, 392 out of 23,164 (1.7%) who actually have moderate (>50%) stenosis, will be missed **(Table 3)**.

Model development and performance severe (>70%) stenosis

Table 2B presents the final model for severe (>70%) stenosis, including age, sex, HDL cholesterol, systolic and diastolic blood pressure, and smoking. The calibration of the model was good, confirmed by a non-significant Hosmer and Lemeshow test (P=0.11). The model discriminated well between participants that did have severe (>70%) stenosis and the participants that did not have severe (>70%) stenosis, with an AUC after correction for over optimism of 0.79 (95% CI, 0.76 to 0.83). Bootstrapping gave a shrinkage factor of 0.95 for the severe (>70%) stenosis model.

Clinical application severe (>70%) stenosis

In the very low risk category (n=15,754) the prevalence of severe (>70%) stenosis was 0.1% and the prevalence in the high risk group (n=1,688) was 3.4%. Using an absolute risk threshold of ≥1.0% (moderate risk) would mean that almost 18% of the population (4,199 out of 23,706) would be identified as being at risk for severe (>70%) stenosis in whom 93 (2.2%) participants would ultimately be diagnosed with severe (>70%) stenosis. Conversely, 34 (0.2%) who actually have severe (>70%) stenosis, will not be screened **(Table 3)**.

Additionally, we checked the discrimination of the model in the individual. The AUC and calibration (confirmed by non-significant Hosmer and Lemehow-tests) was good in the different cohorts, as well as the classification of the individuals in the cohorts in risk categories **(Appendix, Table 1)**.

In our previous cost effectiveness analyses we indicated that screening could be worthwhile in 65-year old men with a prevalence of severe (>70%) stenosis of at least 3% and in 75-year-old women with a prevalence of severe (>70%) ACAS of at least 5%. (de Weerd et al. Submitted). Therefore, we applied the model of severe (>70%) stenosis in 60-69 year-old men and in 70-79 year-old women **(Table 4)**. In on average 65-year-old men we were able to identify 375 men with a high risk of having severe (>70%) stenosis, of these 11 men (2.9%) did actually have severe (>70%) stenosis. In on average 75-year-old women we identified 196 participants with a high risk for having severe (>70%) stenosis. Of these women 6 (3.1%) did actually have severe (>70%) stenosis.

Table 2A. Prediction model for the presence of moderate (>50%) stenosis

Variable	Regression coefficient (unadjusted)	Regression coefficient (adjusted) *	Odds Ratio	SE
Age	0.073	0.072	1.076	0.000
Gender	0.282	0.276	1.326	0.114
HDL cholesterol	-0.536	-0.525	0.585	0.000
LDL cholesterol	0.099	0.097	1.104	0.039
Triglycerides	0.119	0.117	1.126	0.012
Systolic BP	0.027	0.026	1.028	0.000
Diastolic BP	-0.043	-0.042	0.958	0.000
BMI	-0.031	-0.030	0.969	0.012
WHR	1.384	1.356	3.99	0.017
Smoking	0.835	0.818	2.304	0.000
Intercept	-9.988	-9.788		
			CI low	**CI high**
Area under the ROC curve*	0.815		0.797	0.833

sf=0.98
* adjusted for overoptimism

Absolute risk for presence of moderate stenosis= $1/(1\text{-}exp^{-[-9.788+[0.072*age]+[0.276 \text{ if men}]-[0.525*HDL\ cholesterol]+[0.097*LDL\ \ cholesterol]+[0.117*Triglycerides]+[0.026*Systolic\ BP]-[0.042*Diastolic\ BP]-[0.030*BMI]+[1.356*WHR]+[0.818 \text{ is smoking}]})$

Table 2B. Prediction model for the presence of severe (>70%) stenosis

Variable	Regression coefficient (unadjusted)	Regression coefficient (adjusted) *	Odds Ratio	SE
Age	0.091	0.086	1.095	0.012
Gender	0.896	0.851	2.451	0.205
HDL cholesterol	-0.734	-0.697	0.480	0.254
Systolic BP	0.032	0.030	1.033	0.005
Diastolic BP	-0.035	-0.033	0.965	0.008
Smoking	1.198	1.138	3.314	0.197
Intercept	-13.084	-12.430		
			CI low	**CI high**
Area under the ROC curve*	0.793		0.757	0.829

sf=0.95
* corrected for overoptimism

Absolute risk for presence of severe stenosis=
$1/(1\text{-}exp^{-[-12.430+[0.086*age]+[0.851 \text{ if men}]-[0.697*HDL\ cholesterol]+[0.030*Systolic\ BP]-[0.033*Diastolic\ BP]]+[1.138 \text{ if smoking}]})$

Table 3. Model performance moderate (>50%) and severe (>70%) ACAS Moderate (>50%) stenosis

Category	Number of participants with stenosis (%)	Number of participants without stenosis (%)	SE (%)	SP (%)	NPV (%)	PPV (%)
Very low risk ≤ 5% (n=21,676)	285 (1.3)	21,391 (98.7)	38.3	92.0	98.7	8.7
Low risk 5-10% (n=1,488)	107 (7.2)	1,381 (92.8)	15.2	98.0	98.3	12.9
Moderate risk 10-15% (n=335)	36 (10.7)	299 (89.3)	7.4	99.3	98.2	16.4
High risk ≥ 15% (n=207)	34 (16.4)	173 (83.6)				

NPV=negative predictive value, PPV= positive predictive value, SE=sensitivity, SP=specificity

Severe (>70%) stenosis

Category	Number of participants with stenosis (%)	Number of participants without stenosis (%)	SE (%)	SP (%)	NPV (%)	PPV (%)
Very low risk ≤ 0.5% (n=15,754)	14 (0.1)	15,740 (99.9)	88.9	66.7	100.0	1.4
Low risk 0.5-1% (n=3,753)	20 (0.5)	3,733 (99.5)	73.2	82.5	99.8	2.2
Moderate risk 1.0-2.0% (n=2511)	35 (1.4)	2,476 (98.6)	45.7	93.1	99.7	3.4
High risk ≥ 2.0% (n=1688)	58 (3.4)	1,630 (96.6)				

NPV=negative predictive value, PPV= positive predictive value, SE=sensitivity, SP=specificity

Table 4. Model performance of the prediction model for severe (>70%) stenosis in 60-69 year-old men and 70-79 year-old women.
60-69 year-old men

Category	Number of participants with stenosis	Number of participants without stenosis	SE (%)	SP (%)	NPV (%)	PPV (%)
Very low risk ≤ 5% (n=1,360)	4 (0.3)	1,356 (99.7)	87.9	34.4	99.7	1.1
Low risk 5-10% (n=1,326)	8 (0.6)	1,318 (99.4)	63.6	67.9	99.6	0.9
Moderate risk 10-15% (n=910)	10 (1.1)	900 (98.9)	33.3	90.8	99.4	2.9
High risk ≥ 15% (n=375)	11 (2.9)	364 (97.1)				

NPV=negative predictive value, PPV= positive predictive value, SE=sensitivity, SP=specificity

70-79 year-old women

Category	Number of participants with stenosis	Number of participants without stenosis	SE (%)	SP (%)	NPV (%)	PPV (%)
Very low risk ≤ 0.5% (n=1,114)	2 (0.2)	1,112 (99.8)	92.0	43.5	99.8	1.6
Low risk 0.5-1% (n=796)	5 (0.6)	791 (99.4)	72.0	25.6	98.9	0.9
Moderate risk 1.0-2.0% (n=476)	12 (2.5)	464 (97.5)	24.0	92.6	99.2	3.0
High risk ≥ 2.0% (n=196)	6 (3.1)	190 (96.9)				

NPV=negative predictive value, PPV= positive predictive value, SE=sensitivity, SP=specificity

Discussion

We developed prediction models that allowed accurate identification of participants that might benefit from screening for asymptomatic carotid artery stenosis. We found that age, gender, blood lipid levels, blood pressure levels, and smoking are strong predictors for the probability of having a severe (>70%) ACAS. Using a prediction rule based on 9 easily obtainable predictors, 4% of the participants were identified as being at high risk of severe (>70%) stenosis.

We did not come across studies performed in relation to the predictors of having moderate (>50%) or severe (>70%) ACAS. But there are studies that reported determinants of carotid artery stenosis. They suggested that hypertension, smoking, cholesterol levels, and male gender were associated with carotid artery stenosis[28-30]. Prognostic studies reporting on future risk and the risk of stroke recurrence have appeared however[31-33]. In these studies blood lipids, hypertension and smoking were strong predictors of stroke. While these studies are not completely comparable, it is plausible that we found matching predictors.

The major strength of this study is the large number of individuals that were included in our population-based cohorts. This gave us the opportunity to present a precise and accurate prediction rule. Using bootstrapping techniques, we demonstrated that the prediction rule was robust. The shrinkage factor was close to 1, suggesting a stable model and the calibration after correction for over optimism also was very good (AUC 0.79 for severe (>70%) stenosis). In addition, not all data were available for each participant. We dealt with this using imputation techniques, accordingly we could use all participants instead of only complete cases. This results in a prediction rule with increased precision.

The data used in our analyses were obtained for different purposes some years ago. Although there are differences in the methods of measurement of degree of stenosis between studies we are not concerned about the validity of our prediction model. Regression analyses indicated that different method for determination of stenosis degree was unrelated to the prevalence estimate of moderate (>50%) or severe (>70%) ACAS. Also, analyses within the Tromsø data [9] indicated that the different approaches almost identified the same in categorizing the participants with moderate (>50%) stenosis. The effect of different methods to measure stenosis degree unlikely affects the outcome of the prediction rule.

If our prediction rule would be validated and confirmed in other future studies, this may have substantial implication for clinical practice, i.e., screening for asymptomatic carotid artery stenosis in the general population. Our finding in fact would imply a pre-screening. If patients are having a high probability for having severe (>70%) ACAS according to this prediction rule, then it might be worthwhile

to screen these patients with Duplex ultrasound. If these individuals actually would appear to have severe (>70%) ACAS operating on these individuals might be an option. Individuals identified with a low probability of severe (>70%) ACAS could be advised not to undergo subsequent screening with Duplex ultrasound. A cost-effectiveness study has shown that screening could be worthwhile in 65-year old men with a prevalence of severe (>70%) stenosis of at least 3% and in 75-year-old women with a prevalence of severe (>70%) ACAS of at least 5% (de Weerd et al. Submitted). We checked the model performance for severe (>70%) stenosis in men aged 60-69 years and women aged 70-79 years. In these subgroups our model was able to identify participants with a high probability of having severe (>70%) stenosis. The prevalence of severe (>70%) stenosis was around 3% in both subgroups. Using this tool as a pre-screeningstool in men apparently would allow identification of groups eligible for Duplex screening for severe (>70%) ACAS. In women the prevalence found did not surpass the original threshold identified for screening to become worthwhile. The balance between costs and effects of this pre-screening scenario needs to be established before definite implementation can be decided on.

In conclusion, we developed a clinical prediction rule that allows identification of subgroups with relatively high prevalence of severe (>70%) ACAS. When population screening for ACAS is considered, use of the prediction rule is recommended to identify subgroups in order to reduce the number needed to screen substantially.

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Appendix. Table1. Cohort specific results based on the overall-prediction rule for severe stenosis

CAPS						
Category	Number of participants with stenosis (%)	Number of participants without stenosis (%)	SE (%)	SP (%)	NPV (%)	PPV (%)
Very low risk ≤ 5% (n=4,214)	1 (0)	4,213 (100)	88.9	83.5	100.0	1.0
Low risk 5-10% (n=413)	1 (0.2)	412 (99.8)	77.8	91.6	100.0	1.6
Moderate risk 10-15% (n=260)	2 (0.8)	258 (99.2)	55.6	96.8	99.9	3.0
High risk ≥ 15% (n=169)	5 (3.0)	164 (97.0)				
AUC=0.94 (0.89-0.99)	H&L calibration p=1.0					
MDCS						
Category	Number of participants with stenosis (%)	Number of participants without stenosis (%)	SE (%)	SP (%)	NPV (%)	PPV (%)
Very low risk ≤ 0.5% (n=5,068)	2 (0)	5,066 (100)	60.0	83.1	100.0	0.3
Low risk 0.5-1% (n=665)	2 (0.3)	663 (99.7)	20.0	93.9	99.9	0.3
Moderate risk 1.0-2.0% (n=287)	1 (0.3)	286 (99.7)	0.0	98.6	99.9	0.0
High risk ≥ 2.0% (n=83)	0 (0)	83 (100)				
AUC=0.72 (0.51-0.93)	H&L calibration p=0.267					
Tromso						
Category	Number of participants with stenosis (%)	Number of participants without stenosis (%)	SE (%)	SP (%)	NPV (%)	PPV (%)
Very low risk ≤ 0.5% (n=4,447)	7 (0.2)	4,440 (99.8)	85.4	67.2	99.8	1.9
Low risk 0.5-1% (n=1,181)	6 (0.5)	1,175 (99.5)	72.9	84.9	99.9	3.3
Moderate risk 1.0-2.0% (n=703)	12 (1.7)	691 (98.3)	47.9	95.4	99.6	7.0
High risk ≥ 2.0% (n=328)	23 (7.0)	305 (93.0)				
AUC=0.87 (0.82-0.92)	H&L calibration p=0.904					
CHS						
Category	Number of participants with stenosis (%)	Number of participants without stenosis (%)	SE (%)	SP (%)	NPV (%)	PPV (%)
Very low risk ≤ 0.5% (n=2,025)	4 (0.2)	2,021 (99.8)	93.8	34.7	99.8	1.6
Low risk 0.5-1% (n=1,494)	11 (0.7)	1,483 (99.3)	76.9	60.2	99.6	2.1
Moderate risk 1.0-2.0% (n=1,261)	20 (1.6)	1,241 (98.4)	46.2	81.5	99.3	2.7
High risk ≥ 2.0% (n=1,108)	30 (2.7)	1,078 (97.3)				
AUC=0.72 (0.51-0.93)	H&L calibration p=0.13					

NPV=negative predictive value, PPV=positive predictive value, SE=sensitivity, SP=specificity

Chapter 7

General Discussion

The main objective of this thesis was to assess whether screening for asymptomatic carotid artery stenosis (ACAS) in the general population is worthwhile for the prevention of stroke.

Main findings presented in this thesis

The prevalence of the condition was identified as one of the major drivers of cost-effectiveness of screening, thus accurate prevalence estimates are crucial. Accurate age- and sex-specific estimates on the prevalence of asymptomatic carotid artery stenosis in the general population were difficult to extract from literature. This was because studies used different cut-off points for severe and moderate stenosis and also many studies did not provide sex- and age-specific prevalence numbers. Using individual participant data (IPD) from four population-based cohort studies, we were able to provide age- and sex-specific prevalence estimates. The prevalence of moderate stenosis ranged from 0.5% to 5.7% in men and from 0.3% to 4.5% in women. The prevalence of severe stenosis ranged from 0.1% to 1.6% in men and from zero percent to 0.9% in women[1-5].

Our cost-effectiveness analyses showed that non-invasive screening with Duplex ultrasound followed by carotid endarterectomy appeared cost-effective in 65-year-old men with a prevalence of severe stenosis of 3% or above and in 75-year-old women with a prevalence of severe stenosis of 5% or above. In addition, non-invasive screening with Duplex ultrasound followed by endarterectomy after finding severe (>70%) stenosis and followed by cardiovascular risk factor management (CVRM) after finding moderate (>50%) stenosis appeared cost-effective when the prevalence was at least 0.1% in men aged 40 years and women aged 50 years. Notably, CVRM alone in populations with a moderate carotid (> 50%) stenosis appeared the optimal strategy in terms of cost-effectiveness.

Since our cost-effectiveness analyses indicated potential benefit in populations with a relatively high prevalence of ACAS, we developed a prediction rule that would allow identification of subgroups with such high prevalence of moderate (>50%) ACAS or severe (>70%) ACAS. When population-based screening for ACAS is considered, use of the prediction rule for severe ACAS is suggested to identify subgroups in order to reduce the number needed to screen with Duplex ultrasound substantially.

Population based screening for severe (>70%) carotid stenosis, followed by CEA, yes or no?

Evaluating the costs and the effects of screening followed by carotid endarterectomy when severe (>70%) stenosis was found, the costs appeared acceptable when the prevalence of severe stenosis was at least 3% in men aged 65 years and when the prevalence of severe stenosis was at least 5% in 75-year-old women. As such screening may be considered worthwhile, since the incremental cost-effectiveness ratio fell below 20,000 euro per quality-adjusted life-year (QALY).

Our results clearly do not support a population-based screening for severe (>70%) ACAS followed by subsequent carotid endarterectomy only, in case of severe stenosis (see appendix for Wilson and Junger guidelines). The prevalence of the condition is too low in the general population. Although we have shown that with a prediction rule we can identify subjects with a higher risk of having a severe (>70%) ACAS, the pertaining pre-screening strategy was not taken into account in our cost-effectiveness analyses yet. In addition, the prediction rule has not been validated in other population, a necessary aspect that awaits further research.

Another aspect that deserves attention is that our cost effectiveness analyses have been based using carotid endarterectomy as treatment option for severe (>70%) carotid stenosis. The treatment effects were based on findings in randomised trials. A recent review indicated that despite about a 3% peri-operative stroke or death rate, CEA for asymptomatic carotid stenosis reduced the risk of ipsilateral stroke, by approximately 30% over three years. However, the absolute risk reduction was small (approximately 1% per annum over the first few years of follow up in the two largest and most recent trials) [8]. The trials have all been performed in centers in which the complication rate after carotid endarterectomy (i.e. intraoperative and postoperative risks) was at the low end of the distribution (≤3%), i.e., performed in so-called centers of excellence in surgery[6]. This likely will change once a national screening program is launched.

Also, it should be acknowledged that the trials have been performed in a time period where widespread lipid-lowering drugs and anti-platelet drugs were not used. Since the mid-1980s significant falls have been reported in annual rates of ipsilateral and any territory stroke, associated with isolated medical intervention for asymptomatic carotid artery stenosis[7]. From 2001, average annual rates of ipsilateral stroke among patients receiving CVRM alone fell below those of patients who received carotid endarterectomy in the ACAS trial[8]. Best evidence suggests that cardiovascular risk factor management alone is now best for prevention

of stroke associated with severe (>70%) asymptomatic carotid artery stenosis[7]. In the study in this thesis presented, we also found that cardiovascular risk factor management alone is best for the prevention of stroke. In fact we showed that CVRM only as compared to CVRM and CEA in severe stenosis yield more health gain at lower costs and thus is the dominant scenario. At present carotid angioplasty or stenting is also a treatment option for treatment of severe (>70%) carotid stenosis. However, it seems that this approach has higher procedural costs[9] and similar major complication rates (at least for symptomatic patients)[10].

Population based screening for moderate (>50%) carotid stenosis yes or no?

Evaluating the costs and effects of screening followed by endarterectomy in case of severe (>70%) stenosis and followed by cardiovascular risk factor management in case of moderate (>50%) stenosis, the cost-effectiveness was acceptable when the prevalence of severe stenosis was at least 0.1%.

Importantly, our analyses indicated that the benefit was actually higher when cardiovascular risk factor management only was applied. This is in agreement with the previous reasoning about the benefit of carotid endarterectomy in severe (>70%) ACAS [7].

As such our finding is not entirely surprising, since the group of individuals that is identified has a similar risk as those who end up in the high risk group identified using the SCORE[11] approach. In several studies asymptomatic carotid artery stenosis (ACAS) was a clear risk factor for stroke and a marker of cardiovascular morbidity. Natural history studies showed an annual stroke risk between ~1% and 3.4% amongst persons with moderate (>50%) ACAS[12;13]. Most of these studies focused on the short-term follow up (i.e. 2-3 years), although one cohort study found similar annual rates of ipsilateral stroke over the course of 10 years[14]. Data from the three randomized controlled trials[8;15;16] indicate that the annual risk of stroke in participants with severe ACAS is approximately 3.3%. The 10-year risks of ipsilateral stroke in participants with <50% stenosis was 5.7% and in participants with 50-99% stenosis these 10-year risks were 9.3%[14]. Thus, patients with moderate stenosis (>50%) or severe asymptomatic stenosis (>70%) are at risk for developing a stroke or transient ischemic attack well above at a risk that qualifies for high risk according to the current CVRM guidelines[17]. Clearly, this qualifies as an indication for initiation of blood pressure and lipid-lowering therapy.

Also in this scenario, one may want to exclude subjects with a low risk of having

a moderate (>50%) or severe (>70%) stenosis from screening. Our prediction rule may be suitable for that purpose, yet needs validation. Furthermore, the present scenario using Duplex ultrasound to identify high risk patients should be compared to an approach in which only risk factor measurements (age, gender, smoking, blood pressure, serum lipids are used to identify high risk groups. Such an approach was previously evaluated and apparently initial use of aspirin for 10 years was cost-effective in middle-aged men and women whose 10-year vascular risk is above 7.5%. The addition of statin therapy made it even more cost-effective when the patients 10-year vascular risk before treatments was higher than 10%[18]. In this analysis the 10-year-risks was calculated. Had life-time risks been calculated statin use would likely have appeared cost-effective at lower ages for both men and women.
The results presented in this thesis embody the thus far absent evidence for considered policy decisions or guidelines for specialists and general practitioners. One might oppose to the results presented because it is based on secondary analyses and indirect comparisons and not based on the results of a randomized screening trial. The latter is generally viewed as the best level of evidence.

Trial or not?

In this thesis we have, however, shown that models of screening for asymptomatic carotid artery stenosis in the general population can provide robust insights that cannot be easily obtained in randomized clinical trials. The major advantage of modelling is the opportunity to study specific characteristics of large complicated systems by reducing this system to the components that are assumed to be most important for the study question.
The major advantage of a trial is the certainty that the results are real and not artefacts of a model. Yet, a trial into the benefit of screening for moderate carotid stenosis followed by CRVM on the prevention of cardiovascular events when compared to usual care will need to involve thousands of participants with many years of follow-up, with is a huge logistic effort with tremendous budgetary implications.

Conclusions

Population-based screening for asymptomatic carotid artery stenosis is not cost-effective considering detection of severe stenosis followed by endarterectomy only. We can however identify people at high risk of having severe stenosis for which screening might be cost-effective.
In further research our prediction rule, based on age, gender, HDL-cholesterol, systolic and diastolic blood pressure and smoking should be validated and evaluated in a cost-effectiveness-analysis. When also cardiovascular risk factor management is offered, CEA is no longer appropriate, i.e., carotid endarterectomy made the cost-effectiveness even worse; offering cardiovascular pharmacotherapy becomes the alternative of choice. Whether population based screening for carotid artery stenosis followed by CVRM only would indeed appear cost-effective when compared to other methods such as the SCORE approach should be assessed prior to actual implementation. For now, population-based screening for asymptomatic carotid artery stenosis should not be implemented.

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Chapter 8

Summary

Screening for asymptomatic carotid artery stenosis in the general population is discussed in many countries because of the benefits of carotid endarterectomy found in the three trials. Many factors influence the cost-effectiveness of screening for asymptomatic carotid artery stenosis in the general population. These factors are, the prevalence of carotid stenosis, the costs of the screening-tool, the sensitivity and specificity of the screeningtool and the benefits of the treatments.

In the discussion on the value of population wide screening for asymptomatic carotid artery stenosis, reliable prevalence estimates are crucial. **Chapter 2** describes the prevalence of carotid artery stenosis in the general population, according to age and sex, through a systematic literature review and meta-regression analysis. We searched PubMed and EmBase until December 2007 for studies that reported the prevalence of ACAS in a population free of symptomatic carotid artery disease. Forty studies fulfilled the inclusion criteria. The pooled prevalence of moderate (>=50%) stenosis was 4.2%. The prevalence of moderate stenosis among people aged <70 years was 4.8% in men and 2.2% in women. Among those >=70 years, prevalence increased to 12.5% in men and 6.9% in women. Metaregression showed that both age and sex significantly affected the prevalence of moderate stenosis. The pooled prevalence of severe stenosis was 1.7%. Thus, the prevalence of moderate stenosis increases with age in both men and women, but men at all ages have higher prevalence estimates. The number of studies that allowed meaningful data synthesis of severe stenosis was limited. That is why we performed an IPD meta-analysis.

In **chapter 3**, we assessed the prevalence of moderate and severe ACAS by age and sex using individual participant data meta-analysis of four population based studies (MDCS, Tromsø, CAPS and CHS). We found a prevalence of moderate ACAS that ranged from 0.5% (95%CI, 0.3% to 0.9%) in men aged below 50 years to 5.7 (4.5% to 7.1%) in men aged 80 years and above. For women this prevalence increased from 0.3% (0.1% to 0.6%) to 4.4% (2.8% to 6.8%). Prevalence of severe ACAS ranged from 0.1% (0.0% to 0.4%) in men aged below 50 years to 1.7% (0.8% to 3.4%) in men aged 80 and above. For women this prevalence increased from zero (0.0% to 0.2%) to 0.9% (0.4% to 2.4%). This is useful information in the discussion on the cost-effectiveness of screening which we evaluated in **chapter 4**.

The aim of this analysis was to evaluate the factual cost-effectiveness of screening for ACAS by Duplex followed by carotid computer tomography (CTA) and subsequent endarterectomy in the general population. We developed a Markov model (Monte Carlo Simulation) simulating the histories of cohorts of patients

according to prevalence distribution of grade of stenosis, age, sex and co-morbidity reflecting National survival statistics and stroke occurrence. Screening was considered cost-effective at an incremental cost-effectiveness ratio of €20,000 euro per quality adjusted life year (QALY) gained. The prevalence cut-off value when screening was cost-effective varied with age and sex. It was cost-effective to screen for ACAS in 65-year-old men with a prevalence of ACAS of at least 3%. In 75-year-old women screening was cost-effective for a prevalence of ACAS of at least 5%. These results corroborate the notion that in middle aged and elderly adults screening may only be warranted in subgroups with a relatively high prevalence of ACAS.

In **chapter 5** we evaluated the cost-effectiveness of screening for ACAS while explicity taking cardiovascular risk factor management (CVRM) into account. With a Markov model and Monte Carlo simulation hypothetical cohort of individuals were simulated. We assumed that CVRM would reduce the stroke incidence by 19% in those identified with moderate to severe stenosis, independent of whether or not CEA had been performed. One time screening for ACAS when CVRM was taken into account appeared cost-effective in men with a prevalence of ACAS of at least 5%. In men aged 40 years or above screening was cost-effective for a prevalence of severe carotid stenosis of 0.1% and above. However, the benefit was essentially driven by CVRM. In a population of 45-year-old women screening was cost-effective when the prevalence of severe carotid stenosis was at least 10%. Screening was cost-effective for a population of women aged 50 years and above with a prevalence of severe stenosis over 0.1%. Again all benefit ensued from CVRM. Overall, cost-effectiveness was determined by CVRM, In fact, CEA tended to decrease QALY gain and thus increased the incremental cost-effectiveness ratio. The benefit of population-based screening for ACAS results from CVRM rather than carotid artery desobstruction.

In **chapter 6** we intended to identify individuals for whom one-time screening for ACAS might be cost-effective. We developed a prediction rule for the presence of severe (>70%) and moderate (>50%) stenosis. We used the individual participant records (n=23,706) from four population-based studies again (MDCS, Tromsø, CAPS and CHS). Individuals with prior symptoms of carotid artery stenosis were not part of the original cohorts. We constructed prediction models to estimate probability of moderate (>50%) and severe (>70%) ACAS from participant characteristics with multivariate logistic regression models. We assessed the calibration and discrimination of the models and used bootstrapping to correct for overfitting.

Presence of moderate (>50%) stenosis was related to age, sex, HDL cholesterol, LDL cholesterol, triglycerides, systolic and diastolic blood pressure, body mass index, waist-to-hip ratio and smoking. The area under the receiver operating characteristic curve (AUC) of the prediction model for moderate (>50%) ACAS was 0.82 (95% CI 0.78-0.83). Among participants with a very low absolute risk (92% of the population) the probability of moderate (>50%) stenosis being present was 1.3%. In those with a high absolute risk (0.8% of the population) the probability of moderate (>50%) stenosis being present was 16.4%. The presence of severe (>70%) stenosis was related to age, sex, HDL cholesterol, systolic and diastolic blood pressure, and smoking. The AUC was 0.79 (0.76-0.83). Among participants with a low absolute risk (66% of the population) the probability of severe (>70%) stenosis being present was 0.1% and in participants with a high absolute risk (7% of the population) the probability of severe (>70%) stenosis being present was 3.4%.

In **chapter 7** we discussed the findings reported in this thesis. Based on Wilson and Junger criteria we answered the main question of this thesis whether screening for asymptomatic carotid artery stenosis in the general population is worthwhile for the prevention of stroke. We concluded that population based screening for asymptomatic carotid artery stenosis is not cost-effective considering detection of severe stenosis followed by endarterectomy only. We can however identify people at high risk of having severe stenosis for which screening might be cost-effective. In further research our prediction rule should be validated and evaluated in a cost-effectiveness-analysis. When also cardiovascular risk factor management is offered, CEA is no longer appropriate, i.e., carotid endarterectomy made the cost-effectiveness even worse. For now, population based screening for carotid artery stenosis should not be implemented.

Samenvatting

Screening naar aanwezigheid van asymptomatische vernauwing van de halsslagader in de algemene bevolking wordt in vele landen besproken. Aanwezigheid van vernauwing van de halsslagader verhoogt de kans op beroerte en operatie verlaagt de kans hiervan aanzienlijk. Veel factoren beïnvloeden echter de kosteneffectiviteit van screening naar asymptomatische vernauwing van de halsslagader in de algemene bevolking. Deze factoren zijn, het voorkomen van vernauwing van de halsslagader, de kosten van de gebruikte screeningsmethode, de gevoeligheid van de screeningsmethode en de voordelen van de behandeling.

Precieze prevalentie schattingen van asymptomatische vernauwing van de halsslagader zijn van groot belang voor de discussie naar de kosteneffectiviteit van screening naar asymptomatische vernauwing. In **hoofdstuk 2** beschrijven we de prevalentie van vernauwing van de halsslagader in de algemene bevolking voor leeftijd en geslacht apart. De prevalentie is gedaan, met behulp van een systematisch literatuur onderzoek en meta-regressie-analyse. We hebben gezocht naar studies die rapporteerden over de prevalentie van vernauwing van de halsslagader in een bevolking zonder symptomen van halsslagadervernauwing in PubMed en EmBase over de periode 1966-2007. Veertig studies voldeden aan de door ons opgestelde criteria. De prevalentie van matige (>=50%) vernauwing was 4.2% in mannen en 2.2% in vrouwen. Bij 70 jarigen, steeg deze prevalentie tot 12.5% in mannen en tot 6.9% in vrouwen. De gepoolde prevalentie van ernstige (>70%) stenosis was 1.7%. Met behulp van meta-regressie-analyse toonden we aan dat deze prevalentie door leeftijd en geslacht significant wordt beïnvloed. De prevalentie van matige en ernstige vernauwing steeg in mannen en vrouwen met de leeftijd, en bij mannen kwam op alle leeftijden een vernauwing vaker voor dan bij vrouwen. Het aantal studies met voldoende informatie over ernstige vernauwing was klein, hierdoor was uitsplitsing naar leeftijd en geslacht niet mogelijk. In **hoofdstuk 3**, hebben we daarom de prevalentie van matige en ernstige vernauwing van de halsslagader bestudeerd door middel van het samenvoegen van de individuele deelnemer gegevens van 4 cohorten (MDCS, Tromso, CAPS en CHS). We vonden een prevalentie van matige halsslagadervernauwing die liep van 0.5% (95% betrouwbaarheidsinterval (BI) 0.3% tot 0.9%) in mannen onder de 50 jaar tot 5.7% (BI 4.5% tot 7.1%) in mannen van 80 jaar oud en ouder. Bij vrouwen liep deze prevalentie van 0.3% (BI 0.1% tot 0.6%) tot 4.4% (2.8% tot 6.8%). De prevalentie van ernstige halsslagadervernauwing liep van 0.1% (BI 0.0% tot 0.4%) in mannen onder de 50 jaar tot 1.7% (BI 0.8% to 3.4%) in mannen van 80 jaar oud en ouder. Bij vrouwen varieerde deze prevalentie van nul (BI 0.0% tot 0.2%) tot 0.9% (BI 0.4% tot 2.4%). Dit is bruikbare informatie in de discussie over de

kosteneffectiviteit van screening die we evalueerden in **hoofdstuk 4**.
Het doel van deze analyse was om na te gaan wat de kosteneffectiviteit was van screening naar asymptomatische halsslagadervernauwing , in de algemene bevolking is, vastgesteld met Duplex gevolgd computer tomografische angiographie (CTA) en als er een vernauwing gevonden werd gevolgd door operatie. Om deze vraag te beantwoorden ontwikkelden we een Markov Model (Monte Carlo simulatie) waarin grote groepen van personen met verschillende leeftijden, geslacht, co-morbiditeit en beroertekansen werden gesimuleerd. Screening werd als kosteneffectief beschouwd als the incrementele kosten-effecitiviteits ratio (aantal euro/aantal QALY's) niet boven de €20,000 per QALY (levensjaar in goede gezondheid) kwam.
Wij vonden dat screening kosteneffectief was indien uitgevoerd bij mannen van 65 jaar waarbij ernstige halsslagadervernauwing bij tenminste 3% van deze groep voorkwam. In 75 jarige vrouwen was screening kosteneffectief indien in deze groep de prevalentie van ernstige halsslagadervernauwing tenminste 5% is. Deze resultaten geven aan dat screening alleen in bepaalde groepen zinvol is, en niet bij iedereen.
In **hoofdstuk 5** hebben we de kosteneffectiviteit van screening berekend wanneer we ook cardiovasculair risico management (farmacotherapie) meenamen. Dat wil zeggen dat we in deze analyse het effect bestudeerden van screening op halsslagadervernauwing en indien positief gevolgd door behandeling zoals beschreven in hoofdstuk 4 en indien er sprake was van een 50-70% vernauwing, deze mensen behandeld zouden worden met risicoverlagende geneesmiddelen (cadiovasculair risico management). Dit deden we weer met behulp van een Markov model en Monte Carlo simulaties. In dit model deden we de aanname dat cardiovasculair risico management de kans op een beroerte met 19% verlaagde in mensen waarbij een matige of ernstige halsslagadervernauwing werd gevonden, onafhankelijk van het wel of niet toepassen van operatie (operatie). Deze screening, met cardiovasculair risicomanagement, was kosteneffectief indien toegepast bij mannen vanaf 35 jaar bij wie tenminste 5% een vernauwing had. Bij mannen van 45 jaar oud en ouder, was deze screening al kosteneffectief indien sprake was van een prevalentie van ernstige halsslagadervernauwing van 0.1%. Het voordeel van screening werd met name bepaald door het cardiovasculaire risico management. Voor een groep 45 jarige vrouwen bleek screening kosteneffectief indien de prevalentie van ernstige halsslagadervernauwing tenminste 10% was. Screening was kosteneffectief bij 50 jarige vrouwen met een prevalentie van ernstige halsslagederverkalking van minstens 0.1%. Ook nu kwam het voordeel van de screening door het cardiovasculaire risicomanagement. Operatie maakte

de screening zelfs minder kosteneffectief.
Omdat de kosteneffectiviteit analyses lieten zien dat screening kosteneffectief zou zijn bij mensen met een bepaalde kans op aanwezigheid van halsslagadervernauwing hebben we in **hoofdstuk 6** geprobeerd deze groep te identificeren. We ontwikkelden een voorspelregel voor de aanwezigheid van ernstige slagadervernauwing en matige slagadervernauwing. Hiervoor gebruikten we het cohort met alle individuele deelnemer gegevens van de vier internationale cohorten. We maakten de voorspelregel met behulp van multivariate logistische regressiemodellen. We berekenden de calibratie en discriminatie van de modellen en gebruikten bootstrap-technieken om te corrigieren voor overoptimisme.
De aanwezigheid van matige halsslagadervernauwing was gerelateerd aan leeftijd, geslacht, HDL cholesterol, LDL cholesterol, triglyceriden, systolische en diastolische bloeddruk, quetelet index, middel-heup ratio en roken. Het model kon goed voorspellen welke mensen een grote kans hadden op de aanwezigheid van matige halsslagadervernauwing.
De aanwezigheid van ernstige halsslagadervernauwing was gerelateerd aan leeftijd, geslacht, HDL cholesterol, LDL cholesterol, systolische en diastolische bloeddruk en roken. Ook dit model kon goed voorspellen welke mensen een grote kans hadden op de aanwezigheid van ernstige slagadervernauwing.
In **hoofdstuk 7** hebben we de beschreven resultaten van dit proefschrift bediscussieerd. Gebaseerd op criteria van Wilson and Junger hebben we getracht de hoofdvraag van dit proefschrift te beantwoorden namelijk of screening naar asymptomatische halsslagadervernauwing in de algemene bevolking zinvol is. We concludeerden dat screening in de algemene bevolking niet geïmplementeerd moet worden.

Aantekeningen

Curriculum Vitae

Marjolein de Weerd was born on June 24th, 1980 in Nieuwegein, the Netherlands. In 1998, after graduating her secondary school at the Anna van Rijn College in Nieuwegein, she started studying Health Sciences at Maastricht University in Maastricht, the Netherlands. After obtaining her Master of Science degree specialized in human movement science in 2003, she started working as a team-manager at Altrecht GGZ, department Wier, in Den Dolder. In November 2006, she started the work described in this thesis at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, supervised by Prof. dr. M. L. Bots, Prof. dr. E. Buskens and Dr. ir. J. P. Greving. In October 2009 she obtained her Master of Science in Clinical Epidemiology at Utrecht University. As of March 2010, she works as a researcher at TNO Quality of Life, working on occupational health in Hoofddorp, the Netherlands.

Appendix

Population based screening yes or no?

Wilson and Jungner[1] established a series of WHO criteria that should ideally be fulfilled before considering screening as a public health policy. Using these criteria we will address whether screening for ACAS in the general population is meaningful.

1. Is the disease an important public health problem?

Asymptomatic carotid artery stenosis (ACAS) is an established risk factor for stroke and a marker of cardiovascular morbidity. Natural history studies reflect an annual stroke risk between ~1% and 3.4% amongst persons with ACAS between 50% and 99% [2,3]. Most of these studies focused on the short-term follow up (i.e. 2-3 years). However one cohort study found similar annual rates of ipsilateral stroke over the course of 10 years[4]. Data from the three randomized controlled trials[5-7] indicate that the annual risk of stroke in participants with severe ACAS is approximately 3.3%.

The 10-year risks of ipsilateral stroke in participants with <50% stenosis was 5.7% and in participants with 50-99% stenosis these 10-year risks were 9.3%[4]. Thus, patients with moderate stenosis (>50%) or severe asymptomatic stenosis (>70%) are at risk for developing a stroke or transient ischaemic attack. In fact these individuals' risk is well above the risk that qualifies as high risk according to the current CVRM guidelines[8].

Nevertheless, the prevalence of severe (>70%) stenosis is low ranging from 0.1% to 1.7% in men and from zero percent to 0.9% in women. This results in a low overall stroke risk for the asymptomatic population. The prevalence of moderate stenosis (>50%) in the general populations is ranging from 0.5% to 5.7% in men and 0.3% to 4.5% in women.

2. Is there an effective treatment for the disease?

Because moderate or severe stenosis is one of the risk factors for stroke apparently alleviating stenosis is important in the primary prevention of stroke. There are several options to reduce risk: one option is to perform surgery (carotid endarterectomy), another is to place a carotid stent. However, risk reduction may also be achieved through a systemic treatment, i.e., cardiovascular risk factor management (drug treatment with platelet aggregation inhibitors, lipid-lowering and blood pressure lowering agents).

Notably, carotid endarterectomy itself is associated with intraoperative and postoperative risks. The trials have all been performed in centers in which the complication rate after carotid endarterectomy was at the low end of the

distribution (≤3%), i.e., performed in so-called centres of excellence in surgery[9]. Also, since the mid-1980s there were significant falls reported in annual rates of ipsilateral and any territory stroke, associated with isolated medical intervention for asymptomatic carotid artery stenosis[10]. From 2001, average annual rates of ipsilateral stroke among patients receiving CVRM alone fell below those of patients who received carotid endarterectomy in the ACAS trial[5]. Current evidence indicates that cardiovascular risk factor management alone may be appropriate for prevention of stroke associated with severe (>70%) asymptomatic carotid artery stenosis[10].

3. Are facilities for further diagnosis and treatment available?
Carotid endarterectomy, cardiovascular risk factor management and CTA are available. For each person identified by screening, it is possible to facilitate endarterectomy and/or cardiovascular risk factor management and CTA. In the Netherlands these treatments are fully covered by health insurance. As for the initial costs, CTA and endarterectomy are more expensive than cardiovascular risk factor management[11-13].

4. Is there an identifiable latent or early symptomatic stage of disease?
Yes there is. Obviously moderate asymptomatic carotid artery stenosis meaning atherosclerotic narrowing of the carotid artery exceeding 50% of the lumen diameter[10] precedes more advanced disease. Severe asymptomatic carotid artery stenosis generally means atherosclerotic narrowing of the carotid artery exceeding 60-70% of the lumen diameter[10].

5. Is the technique to be used for screening effective?
Different methods for screening are available. Angiography may not be current practice anymore in many clinics, because it is more expensive and carries an inherent risk of complications[14]. For a population-based screening Duplex ultrasound as the screening tool is the best alternative due to its non-invasive nature without side effects. When Duplex ultrasonography is used, there are still some aspects that need attention, one of which is the technician depended nature of the technique. This may lead to differences in determination of the degree of stenosis despite Doppler flow patterns (peak systolic velocity) are measured in a precisely defined area in the lumen[15].

6. Are the tests acceptable to the population?
The participation rates in the large cohort studies included in this thesis appear

to indicate that Duplex ultrasound is acceptable as a screening test[16-20]. It is a non-invasive screening tool without complications. The diagnostic test which is used to confirm the Duplex when a severe stenosis was found, the CTA, is invasive. This test is only used when a severe stenosis was found using Duplex ultrasound and is used to find whether this patient is eligible for endarterectomy.

7. Is the natural history of the disease known?

Knowledge about the natural history of asymptomatic carotid artery stenosis has been derived from trials in which the effect of carotid endarterectomy was compared with medical treatment. The stroke rate in participants with asymptomatic participants with severe (>75%) stenosis was approximately 3.3% per year[21]. Based on the trials [5,6] the relative stroke risks for severe stenosis is 5.0 and the relative stroke risk for moderate stenosis is 2.0. Additionally, the incidence of stroke in men is higher than the incidence of stroke in women[22] and this has impact on the effectiveness of population-based screening. An overall mean rate of stenosis progression, any change to a higher category of stenosis, was found to be 2.8% annually[23]. The rate of progression was higher for men (3%) than for women (1.5%)[23]. Additionally, findings suggest that participants with coronary artery disease and participants with carotid plaques were independently associated with the incidence and the rate of stenosis progression[23].

8. Is there a strategy for determining which patients should and should not be treated?

It is unthinkable to screen a volunteer, find a stenosis and then offer no treatment at all. However, which treatment to offer may be disputed. Should one offer surgery (carotid endarterectomy), place a carotid stent, or achieve risk reduction by cardiovascular risk factor management (drug treatment with antiplatelet agents, lipid-lowering or blood pressure lowering agents). Thus far, asymptomatic moderate (50-70%) stenosis generally is not treated, but they are at increased risk for developing stroke. Thus, cardiovascular risk factor management seems to be a reasonable approach.

9. Is the cost of screening acceptable?

Evaluating the costs and the effects of screening followed by carotid endarterectomy only, the costs are acceptable when the prevalence of severe stenosis was at least 3% in men aged 65 years and when the prevalence of severe stenosis was at least 5% in 75-year-old women. As such screening may be considered worthwhile, since the incremental cost-effectiveness ratio fell below 20,000 euro per quality-

adjusted life-year (QALY). When the prevalence of severe stenosis was less than 3% in men and 5% in women the cost-effectiveness of screening was not acceptable. We found that the prevalence of severe stenosis ranged from 0.1% to 1.7% in men and in women this prevalence ranged from zero to 0.9%. This prevalence was not enough to render the cost-effectiveness for screening acceptable. The prevalence increased with age, but screening in higher age categories should evidently not only be driven by prevalence alone. Participants at higher ages also have more co-morbidities, which makes the screening and treatment less (cost-)effective.
Evaluating the costs and effects of screening followed by endarterectomy in case of severe (>70%) stenosis and followed by cardiovascular risk factor management in case of moderate (>50%) stenosis, resulted in an acceptable cost-effectiveness when the prevalence of severe stenosis was at least 0.1%. Additionally, when we analyzed the effect of cardiovascular risk factor management only, the QALY gain was higher than the QALYs gained when endarterectomy together with cardiovascular risk factor management was offered. Accordingly drugs render the benefit.
In fact, we showed that CVRM only as compared to CVRM and CEA in severe stenosis yields more health gain at lower costs and thus is the dominant scenario. Screening could in fact be used to find participants at high risk and thus eligible for CVRM. Because, people may also be prescribed additional blood pressure lowering medication this will influence the cost-effectiveness. The initial costs will be marginally higher but because the effects will also be higher the iCER will remain less than 20,000 euro per QALY. Nevertheless, we did not take into account the effect of CVRM on major other cardiovascular events[5]. Whether population based screening for carotid artery stenosis would indeed appear cost-effective when compared to other methods such as serum cholesterol measurements should be assessed prior to actual implementation.

10. Screening should be an on-going process

In this thesis we analyzed one-time screening only, which was not cost-effective when only carotid endarterectomy was offered after severe stenosis was found. Additionally, we showed that screening was highly cost-effective when besides carotid endarterectomy also cardiovascular risk factor management was offered upon diagnosing moderate stenosis was found. In the latter, one-time screening results in life time benefits.

One-time screening when only endarterectomy is offered for severe stenosis does not fulfill the WHO criteria for screening. Based on these analyses we should not

consider screening in the general population. However, we may indeed identify a group of participants with a high risk for severe carotid stenosis. This identification was based on age, gender, HDL-cholesterol, systolic and diastolic blood pressure and smoking. In the identified risk group (7.1% of the population), screening was worthwhile. This group, in which screening appeared cost-effective, consisted of only men. Obviously, it is important to estimate the cost-effectiveness of this "pre-screening" followed by one-time US screening for carotid artery stenosis (compared to no screening at all) before implementation may be suggested.

It seems quite simple to find the people eligible for screening with this prediction rule, you have to estimate the costs made for the people to come.

One-time screening fulfills the WHO criteria for screening if we also offer cardiovascular risk factor management. But, we have to consider the low prevalence numbers of severe asymptomatic carotid artery stenosis, to make the screening worthwhile. Thus, screening is probably not the best option; we should consider population-based cardiovascular risk factor management without screening.

This approach was previously evaluated and apparently initial use of aspirin for 10 years was cost-effective in middle-aged men and women whose 10-year vascular risk is above 7.5%. The addition of statin therapy made it even more cost-effective when the patients 10-year risk without treatments surpasses 10%[24]. Note that 10-year-risks were estimated. Life-time estimates, i.e., extrapolating the cohort simulations to extinction would most likely result in cost-effective scenarios for younger age groups.

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