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Five Year Outcomes in Men Screened for Carotid Artery Stenosis at 65 Years of Age: A Population Based Cohort Study

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WHAT THIS PAPER ADDS

Although screening for carotid stenosis has been debated for decades, there is a shortage of contemporary studies evaluating the natural course of carotid atherosclerosis. This population based observational study shows a surprisingly good prognosis for men with a screening detected plaque and moderate stenosis over a five year period, and indicates that some lesions may even regress with modern medical therapy. However, men with a screen detected severe stenosis have a high risk of neurological events, despite optimum medical treatment. Both of these observations are of great clinical importance.

Objective: This study aimed to determine the outcome of 65 year old men five years after carotid ultrasound screening, as well as risk factors for disease progression.

Methods: All 65 year old men living in the county of Uppsala 2007–2009 were invited to an ultrasound examination of both carotid arteries and re-invited at age 70. The cohort was grouped into normal carotids, plaque without significant stenosis, moderate stenosis (50–79%), and severe stenosis (80–99%). The rate of disease progression was assessed from ultrasound data. Data on mortality, ipsilateral neurological events, risk factors, and medication were obtained from patient records and population registries.

Results: Among men participating in carotid screening at age 65, 3,057 were re-screened at age 70. In those with normal carotids (n = 2,318), 23 (1.0%) progressed to a moderate stenosis, and four (0.2%) to a symptomatic severe stenosis. Among those with plaque (n = 696), 25 (3.6%) progressed to moderate stenosis, and eight (1.1%) to severe stenosis, of whom four (0.6%) had symptoms. Of 31 men with 50–79% stenosis, four (12.9%) had progressed to a severe stenosis, of whom two (6.5%) developed symptoms. Five of twelve subjects (42%) with 80–99% stenosis developed symptoms. Disease regression was present among 289/692 plaque (41.7%) and 16/33 stenosis (48.4%). In multivariable analysis, smoking, coronary artery disease and hypercholesterolemia were associated with disease progression. The proportions of antiplatelet, statin, and antihypertensive treatment in the population at age 70 were 22%, 29%, and 55%, respectively.

Conclusion: Men with plaques and moderate stenosis have a good prognosis, but in those with severe stenosis there is a high risk of neurological events.

Keywords: Atherosclerotic plaque, Carotid stenosis, Mortality, Natural history, Stroke rate
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INTRODUCTION

Stroke is a major cause of death and disability. Approximately one quarter of ischaemic strokes result from embolic events related to carotid artery stenosis.[1] Carotid artery atherosclerotic disease is present in 27–64% of the population, and can be detected easily with ultrasound.[2–4] The present study group has reported previously the prevalence of carotid artery atherosclerotic disease based on a population based screening study performed in men aged 65 in conjunction with abdominal aortic aneurysm screening.[3] Although carotid artery atherosclerotic disease can be detected easily, the natural history of the disease and outcome for individuals participating in screening studies is not well studied. Most previous reports on the natural course of carotid atherosclerosis and risk factors for disease progression are outdated, explore selected populations with several exclusion criteria, and seldom reflect modern treatment standards. Thus, there is a need for updated, contemporary, general population based data.

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Several previous studies have investigated the association between carotid plaque progression and the risk of stroke, indicating a higher risk of cerebrovascular events in individuals with progressive disease. Although most plaques remain unchanged, in historical reports approximately 20% progress to a more severe stenosis or occlusion over time.[5]

Previous studies have shown that carotid endarterectomy (CEA) may be an effective treatment in ischaemic stroke prevention in patients with asymptomatic carotid artery stenosis.[6,7] Most individuals with a diagnosed asymptomatic carotid stenosis are treated with best medical treatment (BMT) and risk factor adjustment, while the practice of surgical intervention for asymptomatic carotid stenosis varies significantly between countries.[8] The main issue with adequate treatment of patients with asymptomatic carotid artery stenosis is to identify the patients with disease progression and high risk of stroke, to facilitate appropriate intervention. In the current report, the outcome was assessed for a cohort of 65 year old men invited to carotid artery screening in 2007–2009. The screened individuals were invited to re-examination after five years. The specific aims were to study the natural course of disease in terms of progression of carotid atherosclerosis, ipsilateral neurological events, and death, and to assess the risk factors associated with disease progression.

METHODS

Between 2007 and 2009 all men born in 1942–1944 in the county of Uppsala, Sweden, attending an abdominal aortic aneurysm (AAA) screening program at the age of 65 years were offered an additional duplex ultrasound examination of the carotid arteries (the index examination of the primary screening cohort). A total of 4,657 subjects participated in primary screening. Of these, 3,488 (75%) had normal arteries, 1,169 (25%) had larger plaque, and 94 (2%) had a stenosis.[3] Between 2012 and 2014 a subset of the cohort was re-invited at the age of 70 years for a new duplex ultrasound (DUS) of the carotid arteries (re-screening). The present study cohort consists of all men born in 1942–1944 attending carotid screening at age 65, who had carotid specific follow up data five years later. This includes those attending re-screening at age 70, as well as those who had undergone carotid surgery during the follow up period. Data on mortality and stroke rates were collected for the entire primary cohort including the non-attending and non-invited subgroups.

DUS examinations were performed at the same quality certified vascular laboratory at age 65 as well as 70. All scans were performed by the same experienced technicians, using the same two machines, both at the 65 year and 70 year screenings (Acuson Sequoia system, Acuson, Mountain View, CA USA), using an L9–4 MHz linear transducer or a Philips I U22 system (Philips Ultrasound, Bothell, WA USA), using an L9–3 MHz linear transducer). Throughout the study, a carotid plaque was defined as a focal intimal-media thickening (IMT) of $\geq 2 \times 6$ mm. Carotid stenosis was classified according to the European Carotid Stenosis Trial (ECST) definition (modified by Jogestrand) as 50–79% or 80–99%.[9–11] This corresponds to 12–60% NASCET stenosis and 65–99% NASCET stenosis, respectively. When the primary screening at age 65 years was done in 2007–2009, all centres in Sweden used the ECST measurement method. The NASCET method was thereafter gradually introduced, and now dominates, although some Swedish centres still use the ECST method. To facilitate comparison, in the present study, the same definition was also used at the re-screening at age 70. Those who underwent CEA between ages 65 and 70 (caused by either symptomatic or asymptomatic disease) were identified in the Swedish Vascular registry. International validations of the Swedvasc registry have shown excellent external validity.[12]

Information on smoking habits, medical history, and current medication was registered at ages 65 and 70 years. Smoking status was classified as never, former, current, and ever (former + current). Medical history consisted of coronary artery disease (CAD), defined as a history of angina pectoris or myocardial infarction, cerebrovascular disease (CVD) as a history of stroke or transient ischaemic attack (TIA), hypertension as a history of hypertension or current antihypertensive medication, and diabetes mellitus as a history of diet or medically treated diabetes. The incidence of ipsilateral neurological events (amaurosis fugax, TIA, or stroke) during the follow up period was collected from patients' records at age 70. Use of statins (ATC-code C10A A) and antiplatelet agents (B01AC) were recorded. All individuals with screen detected stenosis >50% at index examination were contacted by a physician and individualised risk factor adjustment (smoking cessation, medication for hypertension and diabetes)[13,14] was recommended along with BMT (antiplatelet agents and statins). Follow up was conducted by primary care physicians.

Individuals with severe carotid artery stenosis (80–99%) were offered a discussion with a vascular surgeon regarding a possible surgical intervention with CEA, based on the patient's preferences. During the entire study period (2007–2014), there was a change in routine of treatment for asymptomatic carotid stenosis towards best medical treatment and risk factor adjustment alone, and all CEAs for asymptomatic disease were performed before the end of 2010. No other intervention (such as stenting) was performed in this cohort.

The screening population was divided into four groups based on the findings of the index examination: 1) normal carotid examination, 2) plaque or insignificant stenosis (<50%), 3) moderate stenosis 50–79%, or 4) severe stenosis (80–99%). Subjects with bilateral disease were classified according to the side with most severe disease. Each subject was included only once in the analysis based on this classification. Individuals with occlusion were excluded from the primary cohort because of uncertainties over whether the occlusion was caused by atherosclerosis or other causes such as dissection.

Disease progression/regression was defined as transformation to another group, with more extensive or less extensive atherosclerotic disease at time of rescreening, and reported as percentage of those attending rescreening,

or follow up because of ICA surgery. Those with ICA surgery were classified as having severe disease not prone to regression. Symptomatic carotid stenosis was defined as a carotid stenosis with ipsilateral neurological symptoms.

Mortality data were retrieved from the National Population Registry for the full cohort invited to screening, including non-attendees at index examination. Five year mortality rates were calculated for the different subgroups and compared with the overall mortality of the entire cohort.

Statistical evaluation of the data was carried out with a computer software package (SPSS PC version 23, Chicago, IL, USA). Differences in proportions were analysed with uncorrected chi-square test or Fisher's Exact test, and results are presented with 95% CI. To estimate the OR for factors associated with ICA atherosclerosis, all variables with a p value $< .1$ in the univariable analyses (Pearson chi-square test) were explored in a multivariable logistic regression model. A p value $< .05$ was considered to be significant. The study was approved by the ethics committee of the Uppsala/Örebro Region. All subjects gave written informed consent prior to the investigation.

RESULTS

Detailed screening results at 65 years of age were published in 2014.[3] The study population is described in Fig. 1 and Table 1. Disease development is presented in Fig. 2 and Table 2. Risk factors associated with progression of carotid atherosclerotic are shown in Table 3. Univariable analysis showed a trend for smoking, CAD, hypertension, hypercholesterolemia, TIA/stroke, and diabetes being associated with no regression, but in a multivariable analysis the significance of these associations was lost.

The five year cumulative neurological event rate was 0.2% in men with baseline normal carotid arteries, 0.6% in men with plaque, 6.5% in men with stenosis of 50—79%, and 42% in men with stenosis of 80—99% (average annual event rate of 0.04%, 0.12%, 1.3%, and 8.4%, respectively). Of those with plaque and/or moderate stenosis, only six subjects (0.8%) had TIA/minor stroke and none had disabling stroke. A total of 571 men (19.0%, 95% CI 17—20) had disease progression after five year follow up. Of 486 subjects with unilateral disease, 11 (2.4%) had no

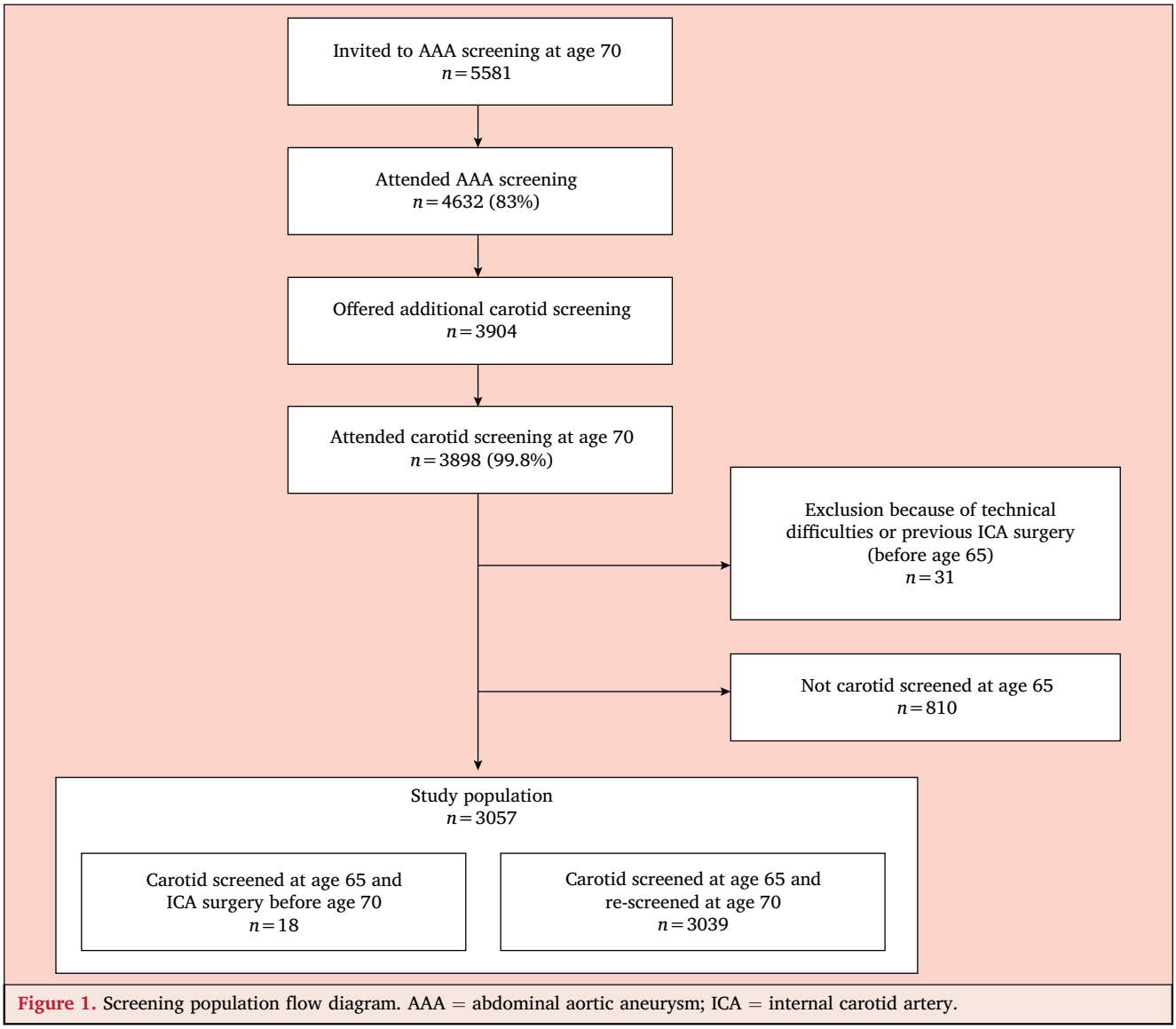

Figure 1. Screening population flow diagram. AAA = abdominal aortic aneurysm; ICA = internal carotid artery.

Table 1. Study population basic characteristics

	At age 65 (n = 3,057)	At age 70 (n = 3,057)	p value
ICA plaque	696 (22.8)	888 (29.0)	<.001
ICA stenosis	43 (1.4)	68 (2.2)	<.001
ICA surgery during five year follow up		18 (0.6)	
Smoking (ever)	1898 (62.1)	1898 (62.1)	1
Smoking (current)	338 (11.1)	255 (8.3)	<.001
CAD	283 (9.3)	371 (12.1)	<.001
Hypertension	1319 (43.1)	1689 (55.3)	<.001
Hypercholesterolaemia	903 (29.5)	1062 (34.7)	<.001
Claudication	23 (0.75)	42 (1.4)	<.001
COPD	190 (6.2)	231 (7.6)	<.001
Diabetes mellitus	334 (10.9)	436 (14.3)	<.001
Antiplatelet agents	428 (14.0)	653 (21.4)	<.001
Statins	691 (22.6)	888 (29.0)	<.001

Data are presented as n (%). CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; ICA = internal carotid artery.

progression, while of 253 subjects with bilateral disease, 16 (6.3%) had no progression (p = .005). Among the 60 men who progressed from normal or plaque status at initial examination to carotid stenosis at five years, eight (13.3%, 95% CI 6.9—24.2) developed neurological symptoms (annual rate 2.6%). Eighteen subjects underwent CEA during the five years after primary screening, of whom 14 (78.0%, 95% CI 55.0—91.0) were operated on because of symptomatic carotid stenosis (Fig. 2). Disease regression was present among 289/692 plaque (41.7%) and 16/33 stenosis (48.4%).

All cause mortality in the cohort attending the five year follow up scan was 3.4%. The five year mortality rate was 3.3% (95% CI 2.8—3.9) among men with normal carotid arteries at age 65, 3.5% (95% CI 2.5—4.7) among those with carotid plaques, and 6.6% (95% CI 2.6—15.7) when a 50—79% carotid stenosis was present (p = .428). None of those with severe stenosis died. Only two subjects had stroke listed as the primary cause of death. All cause mortality among those who did not attend the five year follow up scan was 13.0% (95% CI 11.3—14.9), significantly higher than for attendees (p < .001).

General use of medical therapy was higher at rescreening (70 years of age) compared with primary screening (65 years). At age 65 years, 433 subjects (14%) were treated with antiplatelet agents, 694 (22%) with statins, and 1,321 (43%) with antihypertensive medication, while at age 70 years, 657 subjects (22%) were treated with antiplatelet agents, 890 (29%) with statins, and 1,692 (55%) with antihypertensive medication (p < .001). Among those with progressive disease, 123 (23%) had antiplatelet agents, 175 (33%) had statins, and 301 (57%) had antihypertensive medication. Details of use of statins, antiplatelet agents, and antihypertensive medication in subgroups are presented in Table 4.

DISCUSSION

This population based longitudinal screening study shows a high prevalence of carotid atherosclerosis among 70 year

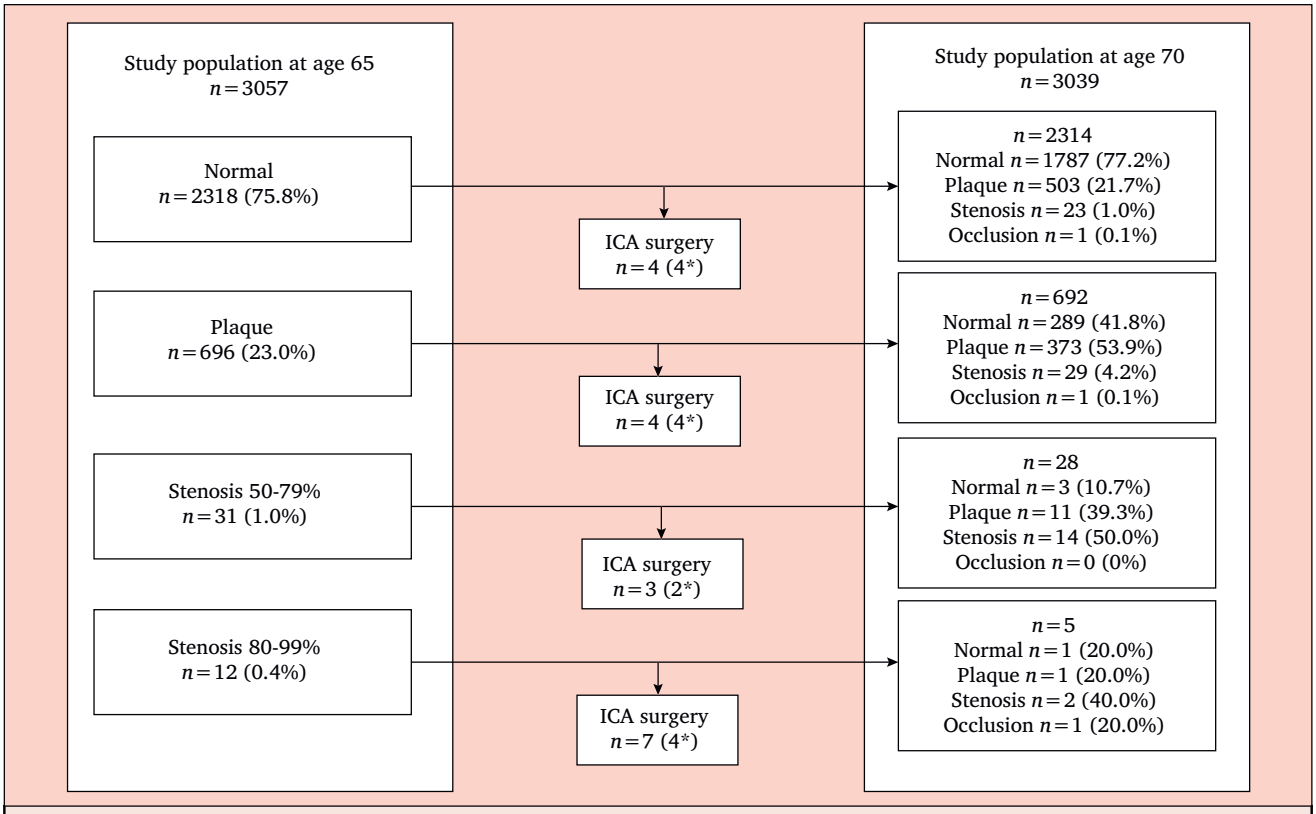

Figure 2. Natural history of study population. *Symptomatic disease. ICA = internal carotid artery.

Table 2. Five year carotid artery disease progression of the study population

At age 65	At age 70			
	Stenosis <50%	Stenosis 50–79%	Stenosis 80–99%	Occlusion
No plaque (*n*=2318)	2,290 (98.8)	22 (1.0)	4 (0.17)	1 (0.04)
Plaque, no stenosis (*n*=696)	662 (95.2)	25 (3.6)	8 (1.1)	1 (0.1)
Stenosis 50-79% (*n*=31)	14 (45.2)	13 (41.9)	4 (12.9)	0
Stenosis 80-99% (*n*=12)	2 (16.7)	0	9 (75.0)	1 (8.3)

Data are presented as *n* (%).

Table 4. Medication at age 70

Carotid status development since age 65	Antiplatelet agents	Statins	AHT
Normal carotid arteries without progress	314 (18.0)	439 (24.2)	907 (51.4)
Normal carotid arteries with progress	123 (23.1)	175 (32.8)	210 (39.4)
Plaque without progress	117 (31.1)	150 (40.0)	256 (69.1)
Plaque with progress	10 (33.3)	14 (46.7)	19 (63.3)
Stenosis without symptoms	12 (22.6)	19 (35.8)	32 (60.4)
Stenosis with progress to symptoms	5 (62.5)	6 (75.0)	7 (87.5)
All with regression	81 (26.5)	95 (31.0)	183 (59.8)

Data are presented as *n* (%). AHT = antihypertensive medication.

old men, but a low prevalence of carotid stenosis. Almost one in five of those without carotid artery disease at age 65 had developed carotid atherosclerotic lesions during the five year follow up, but only 2.0% had developed a significant (>50%) stenosis. Furthermore, 41.4% of those with atherosclerosis at 65 showed disease regression, which improved their status despite the fact that they were five years older.

Only a very small proportion progressed to clinically significant disease with neurological events among individuals with normal carotid arteries, plaque, or moderate stenosis at age 65. Conrad et al. studied the natural history of 794 patients with moderate stenosis and showed a five year plaque progression rate of 39% and a 2.3% annual ipsilateral neurological event rate.[13] Both progression and event rates were much higher compared with the present study, which found a disease progression rate of 19%, and an annual neurological event rate of 1.3% among men with moderate stenosis. This however can be explained partly by a different and wider definition of plaques in the present report. Furthermore, Kakkos et al.[5] investigated progression of asymptomatic carotid artery stenosis among 1,121 patients with 50–99% stenosis and found a progression rate of 20%, similar to the findings of this investigation. The present study shows that smoking, CAD, and hypercholesterolemia were the only risk factors associated with progression of atherosclerosis. Of the well documented and adjustable risk factors for stroke,[14,15] none showed an association with neurological events. This may be explained by the cohort with symptomatic disease being too small, with a risk of type II statistical error.

An interesting finding was the relatively high regression rate of 41.4% in the present study, consistent with the regression rate of 50.1% showed by Spence et al. among 4,378 referral patients.[16] A large percentage of subjects in this group were on antihypertensive treatment, whereas treatment with antiplatelet agents and statins was less common, 26.5% and 31.0%, respectively. In the present study the rate of regression was similar regardless of the severity of the disease. To fully understand this finding, more extensive evaluation is needed, exploring risk factors and the point in time that the subjects received BMT, and this will be evaluated in a separate study.

The five year all cause mortality in this screening cohort was 3.4%. Only two subjects had stroke listed as their primary cause of death, indicating that most individuals died

Table 3. Risk factors for development of carotid atherosclerosis

Risk factors at age 65	Normal at at age 70 (*n* = 2460)	Atherosclerosis at age 70 (*n* = 589)	Bivariable analysis	Multivariable analysis	
			p value	OR (95% CI)	*p* value
Smoking (ever)	60 (58–62)	69 (65–73)	<.001	1.4 (1.2–1.8)	.001
Never	40 (38–42)	31 (28–35)	<.001		
Current	8 (7–9)	11 (9–14)	.006		
Former	52 (50–54)	57 (53–61)	.015		
Coronary artery disease	11 (10–12)	17 (14–21)	<.001	1.3 (1.0–1.8)	.034
Hypertension	55 (53–57)	58 (54–63)	.168		
Hypercholesterolaemia	33 (31–35)	42 (38–46)	<.001	1.3 (1.1–1.6)	.008
Stroke/transitory ischaemic attack	6 (5–7)	7 (5–9)	.818		
Claudication	1 (1–2)	2 (1–3)	.259		
COPD	8 (7–9)	8 (6–10)	.956		
Diabetes mellitus	14 (12–15)	16 (13–19)	.094	1.0 (0.8–1.3)	.806

Data are presented as medians (interquartile range). COPD = chronic obstructive pulmonary disease; OR = odds ratio; CI = confidence interval.

from other causes. All cause mortality among subjects who did not attend the five year follow up scan was 13%, which suggests a much greater morbidity in this group. This finding, that individuals who do not accept an invitation to screening have higher mortality, is expected, and has been shown in relation to mammography screening[17] and AAA screening.[18] Yet, this fourfold increase of mortality was greater than expected. Subgroup analysis showed that individuals with stenosis had higher all cause mortality than subjects with normal arteries or plaque. In a recent systematic review, Giannopoulos et al. found a five year all cause mortality in patients with asymptomatic carotid stenosis as high as 24%. However, this finding was based on cohorts with a broader age span in which different proportions of patients were on statin treatment, and no information was presented on other forms of BMT or risk factor adjustment.[19]

Antiplatelet therapy and statins have long been the therapy of choice for stroke prevention in individuals with carotid stenosis.[20–22] A recent review by Rothwell et al. confirmed that medical treatment reduces the risk of stroke substantially, identifying antiplatelet agents as the key intervention.[23] Several studies have also shown that atherosclerotic plaque progression increases the risk of stroke.[24] In the present study, among men with 50–79% stenosis, only two subjects developed symptoms, which suggests a benign development or that BMT and risk factor adjustment is effective stroke prevention in this subgroup. Among individuals with 80–99% stenosis, 42% developed symptoms, suggesting a need for additional therapy. Medical treatment was more common among those with carotid atherosclerosis, but was not associated with disease progression.

A recently published model study showed that screening for asymptomatic carotid stenosis was cost effective given preventive intervention would reduce the risk of stroke, with at least 22% among subjects with screen detected ACAS.[25] Several studies show that a probable stroke risk reduction with modern BMT is around 50%, which suggests that screening could be cost effective. Assuming effect size of BMT, a 65 year old man would, on average, gain 0.44 stroke free years by taking part in a screening program. Each prevented stroke resulted in a mean 6.5 additional stroke free years for the individual who avoided a stroke. However, modern BMT not only lowers the risk of stroke, but also prevents general cardiovascular morbidity and mortality. With such an effect taken into account, the gain of screening would be even greater. General population screening is not recommended in the 2017 ESVS Guidelines.[26] The observed low prevalence of significant screen detected ICA stenosis and generally relatively benign natural course of carotid atherosclerotic plaque in the present study support this recommendation. This study, however, also shows that most of those with stenosis and at risk of vascular events are not on preventive treatment despite comorbidity, and thus could potentially benefit from selective screening.[26] Screening with a simplified protocol[11,27] could identify individuals at risk who could be further examined with more extensive evaluation of plaque characteristics and plaque texture features, such as large lipid rich necrotic core (LNRC), a thin or ruptured fibrous cap (FC), the presence of inflammatory cells, ulcerations, and intraplaque haemorrhage (IPH). Depending on plaque features, stroke risk can differ from 1% to 10%.[28] New methods with measurements of total plaque area (TPA)[29] and plaque volume could also identify high risk groups. Thus, it seems reasonable to further explore the potential of selective screening as already suggested by the 2017 ESVS Guidelines.

While this is a general population based study with a high participation rate, it has several limitations. One limitation is the all male cohort, which limits the generalizability to a certain extent. On the other hand, the cohort is a part of an already established screening program and an additional ultrasound examination would be easy to implement.

The questionnaire based design with self reported data is prone to recall bias, which may underestimate the importance of individual risk factors and preventive medication. A limitation in the original study design was that although it was possible to identify all ipsilateral events, differentiation could not be made between TIA and stroke. It is believed, however, that all patients with a symptomatic carotid lesion represent a subgroup of individuals that are at high risk of a major stroke and therefore are in strong need of better preventive treatment.

The low prevalence of carotid artery stenosis makes conclusions about the influence of medical therapy on the natural history of stenosis and stroke prevention difficult, despite the fact that the studied cohort was fairly large. The small number of patients with stenosis and the method used to define the subgroups probably explain part of the observed regression rate; however, it is believed that regression does occur. This is supported by a recent study by van Lammeren et al., who showed temporal changes in the composition of atherosclerotic plaques.[30] Measurement error is another factor that could influence the regression rate, although an inter-observer analysis validating the two technicians who performed all the examinations at both ages 65 and 70 showed very good inter-observer agreement ($\kappa = 0.8$ for greyscale evaluations and $\kappa = 1.0$ for PSV measurements).[11] The higher five year mortality rate among non-attendees indicates that the most comorbid subjects with high risk of carotid disease and those suffering a major stroke probably are overrepresented among non-attendees. Thus, some degree of selection bias is inevitable and is acknowledged.

To fully understand the effect of modern intervention strategies, there is a need for further investigations, preferably in large randomised, controlled trials.

CONCLUSION

Carotid atherosclerotic plaque and low grade stenosis (50–79%) has a relatively benign rate of development over five years. Very few cases progressed to symptomatic disease and were in need of additional treatment. More severe

stenosis (80—99%) has higher rate of neurological events and may benefit from additional treatment.

CONFLICTS OF INTEREST

None.

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COUP D'OEIL

Saccular Aneurysm of the Brachiocephalic Vein

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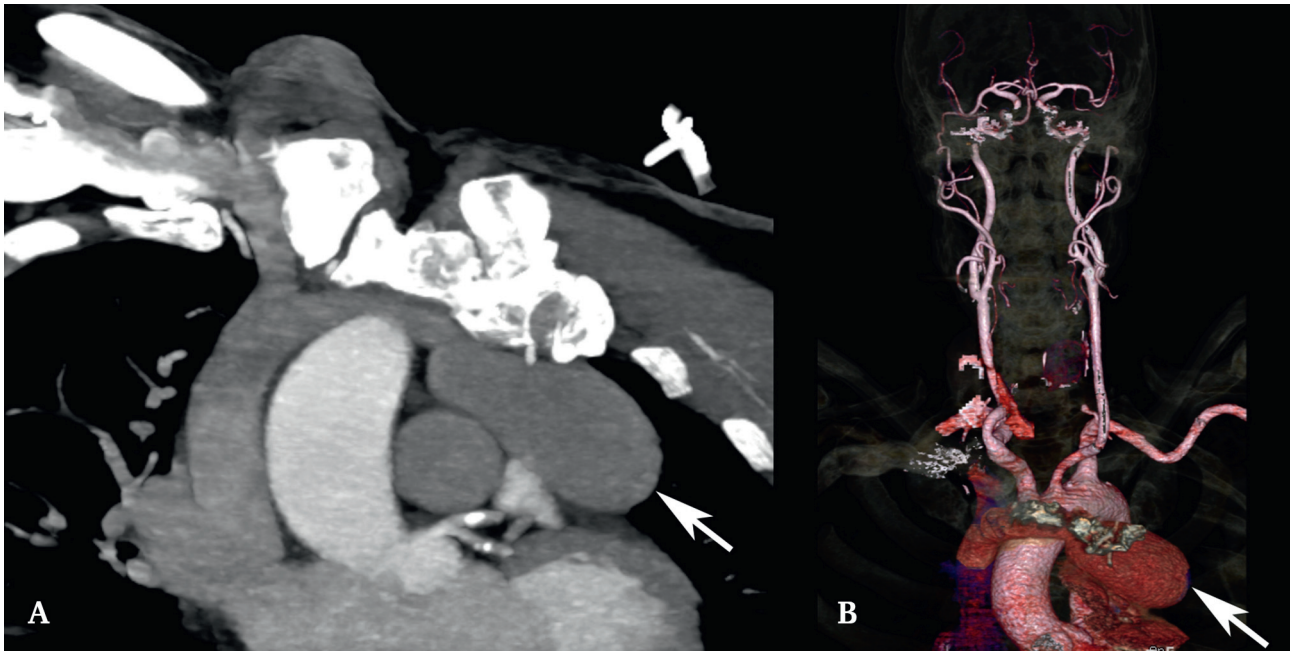

A 74 year old male with a history of atrial fibrillation was admitted to the neurology department with acute onset of vertigo and dysarthria and was treated for a vertebrobasilar stroke. Within two days the vertigo and dysarthria improved significantly. As an incidental finding, a saccular aneurysm of the brachiocephalic vein measuring approximately 7 cm (arrow, A and B) was diagnosed on computed tomography angiography. As the patient had already been treated with a direct oral anticoagulant (apixaban) for atrial fibrillation, no vascular intervention was advocated. Aneurysms of the brachiocephalic vein are extremely rare, with fewer than 20 cases reported in the literature.

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