PERIPHERAL ARTERIAL DISEASE IN THE ELDERLY

W.T. Meijer

PERIPHERAL ARTERIAL DISEASE IN THE ELDERLY

Perifeer arterieel vaatlijden bij ouderen

PROEFSCHRIFT

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Letta Meijer-Rakers (1922-1988)
Peter Meijer (1928-1990)

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Chapter 1

Introduction

Introduction

Largely as a result of an aging population in most developed nations, atherosclerotic cardiovascular disease has become a major health problem.[1-3] Atherosclerosis is the most common cause of peripheral arterial disease (PAD), a chronic occlusive disease of the arterial system distal to the aortic bifurcation. PAD is asymptomatic in the early stages, and when it becomes symptomatic usually presents itself as intermittent claudication: ischemic pain in the calf of the leg induced by walking and relieved by standing still. In approximately 25% of the cases intermittent claudication progresses into critical ischemia.[4-6]

PAD is an important health problem in the elderly; the prevalence increases sharply with age from 3% in those under 60 years to over 20% at 75 years and over.[7] Studies report a wide range of prevalences of PAD, because of different approaches to assess its prevalence. Assessment by the traditional methods (i.e. interview, palpation of peripheral pulses, auscultation to detect femoral bruits) yields low frequencies.[8-11] Assessment with the use of the ankle-arm systolic blood pressure index (AAI), recommended as the best test for field studies,[12] provides prevalences of PAD in the range of 3% to 14% when a threshold value for the AAI between 0.75-0.90 is used.[10,11,13,14] The threshold value for the AAI that prevails in most studies nowadays is 0.90.[15-18] The AAI has been shown to be both reliable and valid when compared to the 'gold standard' angiography,[15,19-21] which itself shows to be far from being the perfect arbiter of disease.[15,22] Also, the prevalence of intermittent claudication varies among studies: from 1% to 7%, partly because of different criteria used.[10,14,16-18,23,24]

Although several earlier studies reported on the prevalence of PAD, studies on the incidence of PAD are (almost) lacking. Apart from important information on the occurrence, such studies would provide the opportunity to detect important determinants for the development of PAD, and facilitate targeted preventive strategies. Identification of prognostic determinants in patients with PAD is relevant, because tools to discriminate between patients likely to progress to serious complications (e.g. limb-threatening ischemia, cardiovascular events) and those who will probably not are virtually lacking. Such prognostic stratification is complicated by the fact that most PAD cases are asymptomatic, and only a minority presents itself with complaints such as intermittent claudication.[6,7,13,16,25] Importantly, the incidence of fatal and non-fatal cardiovascular disease in subjects with asymptomatic PAD seems much higher than in subjects without PAD, and probably is in the same range as subjects with symptomatic PAD (i.e. intermittent claudication).[13,16,25,26] This illustrates the need for the prognostification in medical practice.

The relatively high prevalence of, notably asymptomatic, PAD combined with the poor prognosis of these subjects raises the question whether targeted screening for PAD among the older adults would be worthwhile.

The studies presented in this PhD-thesis are aimed at producing additional empirical data on the issues raised above. The following questions will be addressed:

1. What is the prevalence and incidence of peripheral arterial disease (PAD) in the elderly?
2. What are determinants of prevalent and incident PAD?
3. What is the cardiovascular prognosis in patients with PAD, and which patient characteristics are strong predictors of poor outcome?
4. Is targeted screening for PAD using the ankle-arm systolic blood pressure index (AAI) worthwhile, and which screening strategy is preferable?

Study design

Most studies were performed in a cohort of 6,450 older men and women participating in the Rotterdam Study. The Rotterdam Study is a single-center, prospective, follow-up study of subjects aged 55 years and over, living in the suburb of Ommoord in Rotterdam, the Netherlands. Emphasis is on four areas of research: cardiovascular diseases, neurogeriatric diseases, locomotor diseases, and ophthalmologic diseases.[27] The baseline examinations were carried out between 1990 and 1993, the participants were interviewed at home and were examined twice at the research center. Among other examinations, the ankle-arm systolic blood pressure index (AAI) was measured in all participants. The first follow-up examination took place between 1993 and 1995 (the Rotterdam Study 2). The second follow-up examination (the Rotterdam Study 3) started in 1997 and will last until the end of 1999. Also, clinical follow-up data on fatal and non-fatal endpoints are obtained from the GPs of the participants from 1990 onward.

Outline of the PhD-thesis

The prevalence of PAD and intermittent claudication in the population at large is presented in Chapter 2. The associations between PAD and atherosclerotic risk factors are described in Chapters 3 & 4; Chapter 4 focuses on glucose and insulin as risk factors for PAD. The incidence of PAD and intermittent claudication in the general population

population are described in Chapter 5, while in Chapter 6 a study on the incidence of intermittent claudication in primary care is presented. In the latter study, data from the Dutch National Survey of Morbidity and Interventions in General Practice (NIVEL) were used. In Chapter 7 the cardiovascular prognosis of PAD is assessed with emphasis on the prognostic value of the ankle-arm systolic blood pressure index (AAI). Several targeted screening strategies, to detect PAD by means of the AAI, are compared in Chapter 8. Finally, the results of the studies are discussed and recommendations for future studies are given in Chapter 9.

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Chapter 2

Prevalence of Peripheral Arterial Disease

Manuscripts based on Chapter 2:

Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral arterial disease in the elderly. The Rotterdam Study. Arterioscler Thromb Vasc Biol 1998;18:185-192.

Rutgers D, Meijer WT, Hoes AW, Bots ML, Hofman A, Grobbee DE. Prevalentie van perifere arteriële vaatziekte en claudicatio intermittens bij personen van 55 jaar en ouder: het ERGO-onderzoek. Ned Tijdschr Geneeskd 1998;142:2851-2856.

Introduction

Peripheral arterial disease (PAD) refers to the manifestation of atherosclerosis in the lower limb distal to the aortic bifurcation. When PAD becomes symptomatic, patients often present themselves with complaints of intermittent claudication: 'cramping', 'fatigue' or 'aching' in the calf of the leg, induced by walking, and relieved by standing still. In approximately 25% of cases with intermittent claudication there is a progression into critical ischemia, e.g. rest pain and gangrene, that may eventually lead to amputation.[1,2]

Several studies have demonstrated that patients with PAD, both with and without symptoms of intermittent claudication,[3-5] are at an increased risk of cardiovascular morbidity and mortality compared to subjects without PAD.[4,6-9] In comparison to the number of reports on other manifestations of atherosclerosic disease however, relatively few population-based studies on the prevalence of peripheral arterial disease and intermittent claudication have been performed.

We assessed the prevalence of peripheral arterial disease and intermittent claudication in a large population-based study including 7,715 subjects aged 55 years and over.

Methods

This study is part of the Rotterdam Study, a prospective follow-up study designed to investigate determinants of the occurrence and progression of chronic diseases in the elderly. Emphasis is on four areas of research: cardiovascular diseases, neurogeriatric diseases, locomotor diseases and ophthalmologic diseases. The rationale and design of the study have been described previously.[10]

All individuals aged 55 years and over, living in a suburb of Rotterdam, the Netherlands (a total of 10,275 subjects), were invited to participate in the Rotterdam Study. Baseline measurements comprised an extensive interview at the participant's home and two visits to the research center. The overall response rate was 78% (7,983 subjects; 3,105 men and 4,878 women). Of these, 879 subjects lived in nursing homes.

Intermittent claudication was diagnosed according to the criteria of the WHO/ Rose- questionnaire,[11] which was included in the home interview. The prevalence of intermittent claudication was assessed in 7,715 participants in whom the answers to the Rose questionnaire were available.

Blood pressure was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer at the right brachial artery in sitting position. The presence of peripheral arterial disease was evaluated by measuring the systolic blood pressure level of the posterior tibial artery at both the left and right leg using a 8 MHz continuous wave Doppler probe (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, UK) and a random-zero sphygmomanometer.[12-16] For each leg a single blood pressure reading was taken with the subject in supine position. The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm (ankle-arm index) was calculated for each leg. The lowest ankle-arm index (AAI) in either leg was used in the analysis.[4] In agreement with the approach followed by Fowkes et al[4] and by Schroll and Munck,[17] peripheral arterial disease was considered present when the AAI was lower than 0.90 in at least one leg. The AAI was not determined in 1,533 participants; 824 subjects did not visit the research center, 4 subjects had died before their visit to the center, and in 705 subjects the systolic arm blood pressure (n=7), or the systolic ankle blood pressure (n=559) or both (n=139) were not measured. The characteristics of these 705 individuals did not differ appreciably from the population in which the AAI could be determined. Thus, the AAI was calculated in 6,450 participants (2,589 men and 3,861 women). We excluded 41 participants (0.6%) with an AAI > 1.50, since this AAI usually reflects arterial rigidity preventing arterial compression, leading to spuriously high ankle blood pressure values.

Established cardiovascular risk factors and the presence (or absence) of symptomatic cardiovascular diseases were recorded, and several non-invasive measures of atherosclerosis (notably ultrasound measurements of the carotid arteries and abdominal aorta) were performed.[10] Hypertension was defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.[18] Diabetes mellitus was defined as current use of antidiabetic drugs or a random or post-load serum glucose level greater than 11.0 mmol/l, after an oral glucose tolerance test.[19,20] Subjects were categorized in current smokers, former smokers and those who never smoked. Serum total cholesterol was determined by an automated enzymatic procedure in a non-fasting blood sample.[21] Serum high density lipoprotein (HDL) cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium. Height and weight were measured and body mass index (kg/m^2) was calculated. A history of myocardial infarction and stroke was obtained through direct questioning and considered positive when confirmed by a physician. A history of angina pectoris was assessed using the WHO/ Rose-questionnaire.[11] Left ventricular hypertrophy (LVH) was assessed using a 12-lead ECG, recorded with an ESAOTE-ACTA cardiograph with a sampling

frequency of 500 Hz. The ECG was stored digitally. Electrocardiographic LVH was determined using an automated diagnostic classification system, the Modular Electrocardiogram Analysis System (MEANS), based on voltage, shape and repolarisation criteria.[22,23] Ultrasonography of both carotid arteries was performed with a 7.5 MHz linear array transducer with a Duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, USA), to assess intima-media thickness of the distal part of the common carotid artery and the presence of plaques in the common and internal carotid artery and in the carotid bifurcation, as detailed elsewhere.[24,25] Common carotid intima-media thickness is measured as the mean value of the near and far wall of both left and right carotid artery. Ultrasound measurements of the diameter of the abdominal aorta were taken by way of B-mode ultrasound recordings using a 3.5 MHz linear array probe (Toshiba SSH 60A, Toshiba Medical Systems, Japan) with the patient in supine position.[26]

To compare our prevalence of peripheral arterial disease (PAD) and intermittent claudication with the prevalences reported in other population-based screening surveys, adjusted prevalences were calculated by applying the age and gender distributions and definitions of PAD in these other studies to the Rotterdam Study data set. Prevalence rates were calculated with exact 95% confidence limits. One-way analyses of covariance was applied to determine the statistical significance of the differences in cardiovascular risk indicators and non-invasive measures of atherosclerosis between subjects with and without peripheral arterial disease, adjusted for differences in age between these two groups. All analyses were performed using BMDP software (BMDP Statistical Software, Inc., Los Angeles).

Results

In Table 1, selected characteristics of the study population are given for men and women separately. PAD was present in 19.1% (95% confidence interval (CI) 18.1-20.0) of all participants. The prevalence of PAD in women (20.5%, 95% CI 19.2-21.8) was higher than in men (16.9%, 95% CI 15.4-18.3). The age difference between men and women accounted for most of this difference in prevalence, because the prevalences in five year age categories for men and women were similar. In both men and women a clear increase in prevalence of PAD with age was observed, ranging from 6.6% in the age category 55-59 years to 52.0% in the age category 85 years or over in men, and from 9.5% to 59.6% in the corresponding age categories in women (Figure 1).

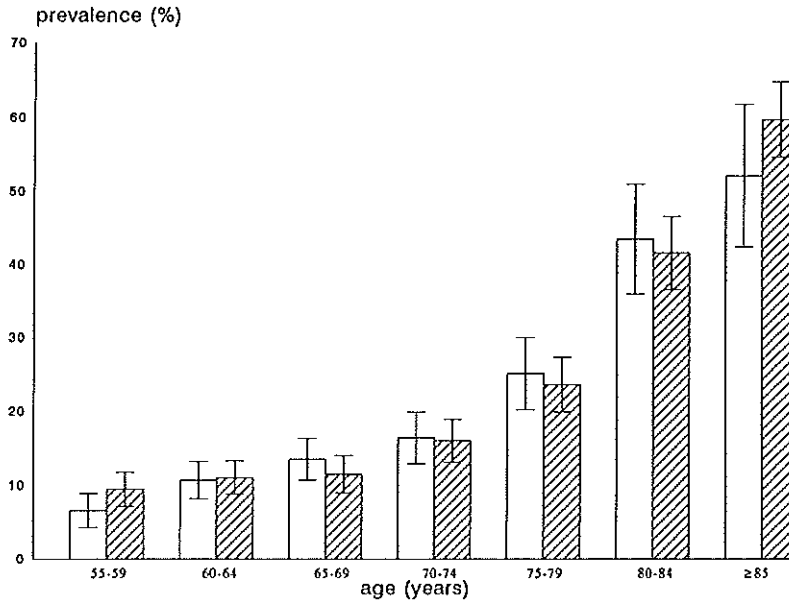

Figure 1. Prevalence of peripheral arterial disease in men (white bars) and women (shaded bars) according to age.

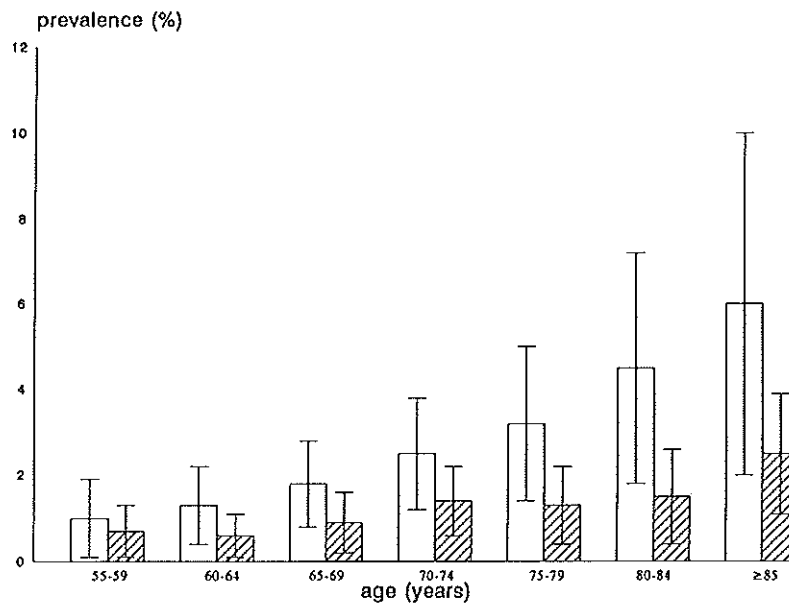

Figure 2. Prevalence of intermittent claudication in men (white bars) and women (shaded bars) according to age.

Intermittent claudication was reported by 1.6% (95% CI 1.3-1.9) of all participants, while the prevalence of intermittent claudication in men (2.2%, 95% CI 1.7-2.8) was higher than in women (1.2%, 95% CI 0.9-1.5). In both men and women a clear increase in prevalence of intermittent claudication with increasing age was present, ranging from 1.0% in the age category 55-59 years to 6.0% in the age category 85 years or over in men, and from 0.7% to 2.5% in the corresponding age categories in women (Figure 2).

Table 1. General characteristics of 7,715 men and women aged 55 years or over in whom the presence of peripheral arterial disease and intermittent claudication was assessed.

Characteristic	Men (n=3,052)	Women (n=4,663)
Age (years), mean (SD)*	69.0 (8.7)	71.7 (10.3)
Body mass index (kg/m^2), mean (SD)	25.7 (3.7)	26.7 (4.1)
Systolic blood pressure (mmHg), mean (SD)	139 (22)	140 (23)
Diastolic blood pressure (mmHg), mean (SD)	75 (12)	73 (12)
Hypertension (%)	26.3	33.2
Diabetes mellitus (%)	10.0	9.9
Smoking (%) Current	30.4	17.5
Former	61.5	27.1
Serum total cholesterol (mmol/l), mean (SD)	6.30 (1.18)	6.81 (1.22)
Serum HDL cholesterol† (mmol/l), mean (SD)	1.22 (0.33)	1.43 (0.37)
Carotid artery‡		
Intima-media thickness (mm), mean (SD)	0.82 (0.15)	0.78 (0.16)
Plaques (%)		
Common carotid	23.3	16.9
Carotid bifurcation	64.2	59.2
History of angina pectoris (%)	6.8	6.9
History of myocardial infarction (%)	12.2	4.3
History of stroke (%)	5.0	4.3

* SD: standard deviation.
† HDL cholesterol: high density lipoprotein cholesterol.
‡ data available of the first 1,660 participants of the Rotterdam Study.[25]

Table 2: Peripheral arterial disease and intermittent claudication in subjects aged 55 years or over.

Intermittent claudication†	Peripheral arterial disease*		Total
	Present (AAI < 0.90)	Absent (AAI ≥ 0.90)	
Men			
present	37	18	55
absent	387	2,117	2,504
Women			
present	36	15	51
absent	706	3,008	3,714
Total			
present	73	33	106
absent	1,093	5,125	6,218

* assessed by measuring the ankle-arm systolic blood pressure index (AAI).
† according to the criteria of the WHO/ Rose-questionnaire.

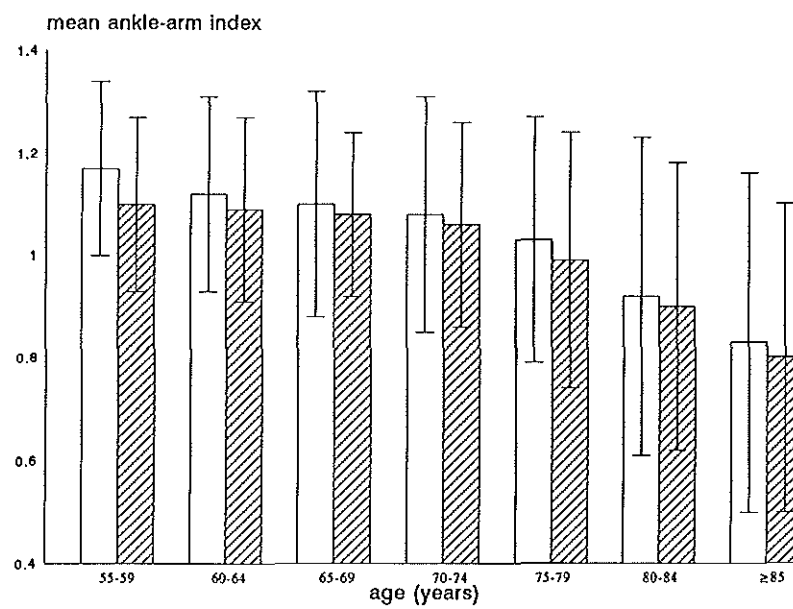

Figure 3. The mean ankle-arm systolic blood pressure index in men (white bars) and women (shaded bars) according to age.

Table 3: Cardiovascular risk indicators in men and women with an ankle-arm index <0.90 or an ankle-arm index ≥0.90, adjusted for differences in age.

Cardiovascular risk factors	Men			Women		
	Ankle-arm index			Ankle-arm index		
	<0.90	≥0.90	*p* value	<0.90	≥0.90	*p* value
Body mass index (kg/m^2), mean	25.2	25.8	0.43	26.6	26.7	0.02
Systolic blood pressure (mmHg), mean	148	137	0.07	150	137	<0.01
Diastolic blood pressure (mmHg), mean	74	75	0.02	74	73	<0.01
Intermittent claudication (%)*	9.5	0.9	<0.01	5.0	0.5	<0.01
Hypertension (%)†	39.4	23.8	<0.01	48.1	29.1	<0.01
Serum total cholesterol (mmol/l), mean	6.28	6.32	0.60	6.97	6.81	<0.01
Serum HDL cholesterol‡ (mmol/l), mean	1.19	1.21	0.06	1.38	1.46	0.63
Diabetes mellitus (%)	11.9	6.7	0.08	16.0	6.3	<0.01
Smoking (%) Current	37.9	21.4	<0.01	21.5	17.1	<0.01
Former	46.7	62.2	<0.01	25.8	29.0	0.91
Cardiovascular disease or measures of atherosclerosis						
History of angina pectoris (%)	9.3	5.9	0.12	9.2	6.4	0.24
History of myocardial infarction (%)	29.9	17.0	<0.01	15.2	7.4	0.34
History of stroke (%)	9.0	3.6	<0.01	8.4	2.0	<0.01
Carotid artery§						
Intima-media thickness (mm)	0.880	0.804	<0.01	0.830	0.756	<0.01
Plaques (%)						
Common carotid	34.4	20.2	<0.01	35.4	10.8	<0.01
Carotid bifurcation	74.2	59.8	0.01	66.7	52.3	<0.01
Distal abdominal aortic diameter (mm)	23.1	19.3	<0.01	16.8	16.0	<0.01
LVH¶ by ECG# (%)	17.3	9.5	0.05	11.4	4.9	0.01

* according to the criteria of the WHO/ Rose-questionnaire.
† defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.
‡ HDL cholesterol: high density lipoprotein cholesterol.
§ data available of the first 1,660 participants of the Rotterdam Study.[25]
¶ LVH: left ventricular hypertrophy.
# ECG: electrocardiogram.

Of the 1,166 subjects with PAD 73 (6.3%) reported symptoms of intermittent claudication (Table 2). Interestingly, men with PAD more often complained of symptoms of intermittent claudication (8.7%) than women with PAD (4.9%). Of the 106 subjects with symptoms of intermittent claudication according to the Rose criteria, 73 (68.9%) had peripheral arterial disease (PAD) defined as an ankle-arm index (AAI) < 0.90. This proportion was similar in men and women.

The mean ankle-arm systolic blood pressure index (AAI) was 1.05 (standard deviation (SD) 0.23); 1.08 (SD 0.24) in men and 1.03 (SD 0.23) in women. The ankle-arm index decreased sharply with advancing age (Figure 3). The distribution of the AAI (Figure 4) was skewed to the left. In 41 participants (0.6%) an AAI higher than 1.50 was measured. These 41 participants were not included in the other tables or figures.

In Table 3, subjects with and without peripheral arterial disease are compared with respect to the presence of cardiovascular risk factors and disease and non-invasive measures of atherosclerosis. Subjects with an AAI < 0.90 had a more unfavourable cardiovascular risk profile than subjects with an AAI ≥ 0.90.

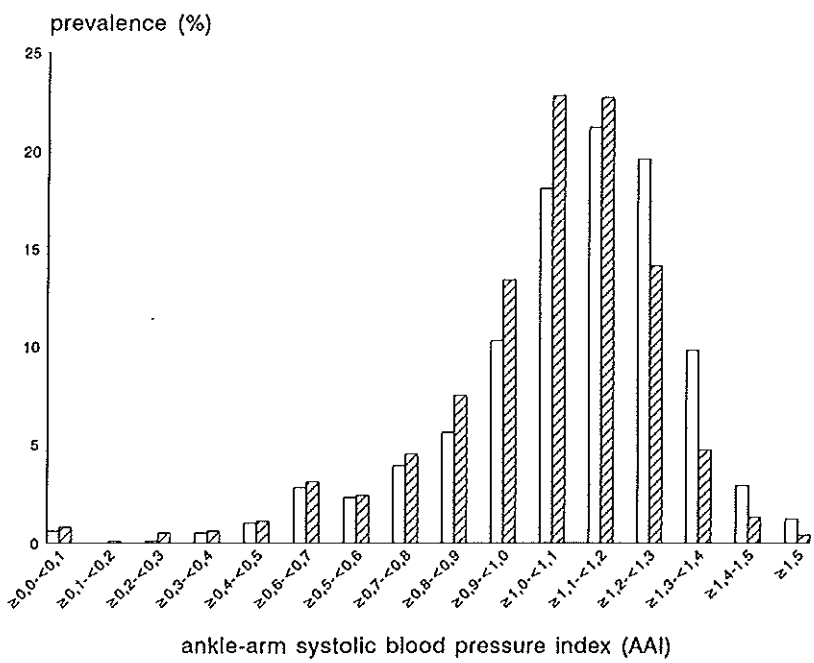

Figure 4. The distribution of the ankle-arm systolic blood pressure index, for men (white bars) and women (shaded bars).

Table 4: Prevalence of peripheral arterial disease in nine population-based screening surveys and in the Rotterdam Study.

Study	Age (years)	Sex	No.	Defin. (AAI†)	Prevalence		Adjusted prevalence*
					%	95% CI‡	%
Meijer et al	≥ 55	Men	2,589	< 0.90	16.9	15.4-18.3	16.9
		Women	3,861		20.5	19.2-21.8	20.5
Stoffers et al[27]	55-75§	Men	1,719	< 0.95	11.0	9.5-12.5	16.5
		Women	1,935		8.6	7.4-9.8	17.0
Newman et al[3]	≥ 65	Men	2,214	< 0.90	13.9	12.5-15.3	22.3
		Women	2,870		11.4	10.2-12.6	26.5
Vogt et al[28]	≥ 65	Women	1,492	≤ 0.90	5.5	4.3-6.7	26.5
Coni et al[29]	>65	Men	112	< 0.75	9.1¶	5.6-12.6	14.0¶
		Women	153		9.1¶		14.0¶
Fowkes et al[4]	55-74	Men	809	≤ 0.90	18.3¶	16.4-20.2	11.6¶
		Women	783		18.3¶		11.6¶
Newman et al[30]	≥ 60	Men	82	< 0.90	26.7¶	20.4-33.0	21.4¶
		Women	105		26.7¶		21.4¶
Hiatt et al[31]	44-68	Men	410	< 0.94	11.9¶	9.8-13.9	13.4¶
		Women	540		11.9¶		13.4¶
Criqui et al[5]	38-82	Men	275	≤ 0.80#	11.7¶	9.2-14.2	8.7¶
		Women	338		11.7¶		8.7¶
Schroll&Munck[17]	60	Men	360	< 0.90	16.0	12.2-19.8	9.7
		Women	306		13.0	9.2-16.8	9.2

* The prevalence was adjusted by applying the age and gender distributions and definitions of PAD in the other studies to the Rotterdam Study data set.
† AAI: ankle-arm systolic blood pressure index.
‡ CI: confidence interval.
§ The age group 45-55 years was not considered in this comparison, the actual studied age group was 45 to 75 years or over.
¶ Prevalence in total population, no separate estimates according to gender were reported.
# Criqui et al. (5) used a different approach to assess the prevalence of peripheral arterial disease; not the standard ankle-arm index (AAI) was used, but four different noninvasive measurements of limb perfusion in the lower extremities.

Table 5: Prevalence of intermittent claudication in thirteen population-based screening surveys and in the Rotterdam Study.

Study	Age (yrs)	Sex	No.	Population	Prevalence		Adjusted prevalence*
					%	95% CI†	%
Meijer et al	≥ 55	Men	3,052	general	2.2	1.7-2.8	2.2
		Women	4,663		1.2	0.9-1.5	1.2
Stoffers et al[27]	55-75‡	Men	1,719	general	1.5	0.9-2.1	1.6
		Women	1,935		2.8	2.1-3.5	0.9
Newman et al[3]	≥ 65	Men	2,214	general	2.0§	1.6-2.4	2.0§
		Women	2,870		2.0§		2.0§
Vogt et al[28]	≥ 65	Women	1,492	rural	7.4	6.1-8.7	1.5
Coni et al[29]	>65	Men	112	rural	6.1§	3.2-9.0	2.0§
		Women	153		6.1§		2.0§
Fowkes et al[4]	55-74	Men	809	general	4.6§	3.6-5.6	1.2§
		Women	783		4.6§		1.2§
Newman et al[30]	≥ 60	Men	82	systolic	6.4§	2.9-9.9	1.8§
		Women	105	hypertension	6.4§		1.8§
Hiatt et al[31]	44-68	Men	410	general/	0.6§	0.1-1.1	1.0§
		Women	540	diabetic	0.6§		1.0§
Smith et al[8]	40-64	Men	18,388	civil servants	0.8	0.7-0.9	0.8
Hale et al[36]	≥ 65	Men	621	general	14.4	11.6-17.2	2.9
		Women	1,082		14.1	12.0-16.2	1.5
Criqui et al[5]	38-82	Men	275	general/	2.2	0.5-3.9	2.0
		Women	338	dyslipidemic	1.7	0.3-3.1	1.0
Reunanen et al[37]	30-59	Men	5,738	general	2.1	1.7-2.5	1.0
		Women	5,224		1.8	1.4-2.2	0.6
Schroll&Munck[17]	60	Men	360	general	5.8	3.4-8.2	1.0
		Women	306		1.3	0.0-2.6	0.6
Hughson et al[38]	45-69	Men	1,716	general	2.2	1.5-2.9	1.4
	50-69	Women	1,535		1.2	0.7-1.7	0.7

* The prevalence was adjusted by applying the age and gender distributions and definitions of PAD in the other studies to the Rotterdam Study data set.
† CI: confidence interval.
‡ The age group 45-55 was not considered in this comparison, the actual studied age group was: 45 to 75 years or over.
§ Prevalence in total population, no separate estimates according to gender were reported.

In both men and women, hypertension, cigarette smoking and a history of stroke were significantly more frequent among subjects with an AAI < 0.90. Left ventricular hypertrophy (LVH) was more frequent in those with an AAI < 0.90, and similarly, these subjects had an increased common carotid intima-media thickness, a higher frequency of carotid plaques, and a larger distal abdominal aortic diameter.

Discussion

In the population-based Rotterdam Study, the prevalence of peripheral arterial disease was 19.1%, varying from 6.6% in women aged 55-59 years to 59.6% in men aged 85 years or over. Intermittent claudication was reported by 1.6% of the participants, varying from 0.7% in women aged 55-59 years to 6.0% in men aged 85 years or over. Of those with peripheral arterial disease, only 6.3% reported symptoms of intermittent claudication. Compared to those with an AAI ≥ 0.90, subjects with an AAI < 0.90, clearly had an unfavourable cardiovascular risk profile, also with regard to other non-invasive measures of atherosclerosis.

The response rate in the Rotterdam Study of about 78% is within the range of similar surveys, with response rates varying from 59 to 98%.[3-5,17,27-31] Because of a lower response rate in the very old in the Rotterdam Study, the prevalence of PAD and intermittent claudication may have been underestimated for this age group, although in a study by Aronow et al [32] among 1,886 persons, mean age of 82 years, in a nursing home, prevalence of PAD was 29% among men and 23% among women.

We used the ankle-arm systolic blood pressure index (AAI) at rest as an indicator of PAD. In a number of surveys an AAI measurement during exercise or reactive hyperemia test was used.[16,31,33] Hiatt et al [31] concluded that these tests are not as useful as the AAI measured at rest. In analogy with other studies, we used a single measurement of the AAI to define PAD. Taking the mean of consecutive measurements, as for example in the Limburg PAOD Study,[27] would probably reduce the prevalence estimates.

There is no consensus regarding the threshold value for the AAI to define PAD. Most of the published surveys used a threshold value between 0.80 and 0.95,[3-5,17,27,28,30,31] while in one a threshold value < 0.75 was used.[29] Different threshold values result in different prevalences for PAD, as is clearly illustrated by comparing the crude and adjusted prevalence rates in the individual surveys (Table 4). Other reasons for reported differences in prevalence estimates between published studies are differences

in age- and sex-distribution of the screened populations, or the restriction to populations with a higher risk for PAD, such as dyslipidemic,[5] hypertensive [30] or diabetic patients.[31]

Only a minority of the participants with PAD in the Rotterdam Study, 6.3%, reported symptoms of intermittent claudication. Other studies reported figures in the range of 5.3% to 18.9%,[3-5,17,27,28,30,31] with the exception of one study, reporting a prevalence as high as 37.5%.[29] This prevalence of 37.5% observed by Coni et al [29] should be interpreted with caution, however, because in this study the strict Rose-criteria were not used to assess the presence of intermittent claudication. The relatively low proportion of PAD patients with complaints of intermittent claudication can partly be explained by the fact that many elderly people do not walk far enough to experience symptoms of intermittent claudication, because of either impaired vascularization of the extremities or other typical disorders, such as osteoarthritis. Of interest is that women with PAD less often reported symptoms of intermittent claudication (4.9%) than men with PAD (8.7%). Possibly, women more frequently present atypical symptoms from ischaemic disease than men, in analogy with observervations in coronary heart disease.[34,35]

PAD is often considered an indicator of generalized atherosclerosis, and as such associated with a poor cardiovascular prognosis. This appeared to be true for participants of this study, as illustrated by the relatively unfavourable cardiovascular risk profile of those with an ankle-arm index lower than 0.90. From other studies similar findings have been reported,[3,4,6-8,27,28] especially for the association between PAD and hypertension, diabetes mellitus and smoking. The finding of an increased common carotid intima-media thickness, a higher frequency of carotid plaques and a larger diameter of the abdominal aorta (as measures of atherosclerosis) supports the relatively poor prognosis of subjects with an AAI < 0.90.

We conclude that the prevalence of peripheral arterial disease (PAD) in the elderly is high while the prevalence of reported intermittent claudication is relatively low. Both prevalences sharply increase with advancing age. The vast majority of PAD patients reported no symptoms of intermittent claudication. This, together with the high prevalence of PAD and unfavourable cardiovascular risk profile of patients with PAD, illustrates the need to explore the use of the ankle-arm index as a risk indicator in cardiovascular screening and risk profiling in medical practice.

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Chapter 3

Determinants of Peripheral Arterial Disease

Manuscript based on chapter 3:

Meijer WT, Grobbee DE, Hunink MGM, Hofman A, Hoes AW. Determinants of peripheral arterial disease in the elderly. The Rotterdam Study (submitted).

Introduction

Peripheral arterial disease (PAD) refers to atherosclerotic occlusive disease of the arterial system distal to the aortic bifurcation, and is a relatively common disorder in the elderly.[1,2] PAD is a manifestation of generalized atherosclerosis, and life expectancy in patients with PAD is reduced compared to subjects without PAD. This is mainly attributable to an increased incidence of cardiovascular disease,[3-5] both in patients with and without complaints of intermittent claudication.[5-7] Thus, the ankle-arm systolic blood pressure index (AAI), a relatively easy means of assessing PAD, may be considered a marker of generalized atherosclerosis.[8]

Atherosclerosis is a complex multifactorial disease process with manifestations that vary by anatomical location. Risk factors may be divided into two major categories; reversible and irreversible risk factors. Reversible factors for PAD include cigarette smoking and hypertension, while non-reversible factors include age, gender, and genetic factors.[9-13]

The purpose of this study was to assess in a population-based setting which determinants are involved in the etiology of PAD, and to what extent known atherosclerotic risk factors are involved.

Methods

This study is part of the Rotterdam Study, a prospective follow-up study designed to investigate determinants of the occurrence and progression of chronic diseases in the elderly. The rationale and design of the study have been described previously.[14]

Details of the selection of the participants and method of measuring the ankle-arm systolic blood pressure index (AAI) have been described previously.[15] Briefly, in 6,450 subjects (2,589 men and 3,861 women) aged 55 years or over, living in the suburb of Ommoord in Rotterdam, the ratio of the systolic blood pressure at the ankle (measured by means of a 8 MHz continuous wave Doppler probe at the posterior tibial artery), and the systolic blood pressure at the arm (measured by means of a random-zero sphygmomanometer at the brachial artery), was calculated for each leg. The lowest of the two ankle-arm indices was used in the analysis.

In agreement with the approach followed by Fowkes et al [7] and by Schroll and Munck,[12] PAD was considered present when the AAI was lower than 0.90 in at least one leg, a threshold value used in most previous studies.[5,7,12,16,17] In addition to this

conventional threshold value for PAD, we also used an AAI lower than 0.70 to define severe PAD.[7,18]

Possible determinants of PAD were recorded for all participants.[14] Hypertension was defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.[19] Diabetes mellitus was defined as the current use of antidiabetic drugs or a random or post-load serum glucose level greater than 11.0 mmol/l, after an oral glucose tolerance test.[20,21] Subjects were categorized in groups of current smokers, former smokers, and those who never smoked. Total alcohol intake was calculated from beverage specific information obtained by a semi-quantitative food frequency questionnaire. One drink was approximately equivalent to 10 grams of alcohol. A venipuncture was performed, applying minimal stasis, using a 21 gauge butterfly needle. Samples were collected into siliconized Vacutainer tubes containing 3.8% trisodium citrate and centrifuged for 10 minutes at 1,600 g at 4°C. Plasma was separated, subsequently centrifuged for 10 minutes at 10,000 g at 4°C and stored at -80°C before assay. Serum total cholesterol was determined by an automated enzymatic procedure.[22] Serum high density lipoprotein (HDL) cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium,[23] with a minor modification as described by Grove.[24] Plasma fibrinogen level was measured as derived fibrinogen of the prothrombin time assay using Tromborel S as reagent on an Automated Coagulation Laboratory (ACL 300, Instrumentation Laboratory, IJsselstein, The Netherlands).[25] This method correlates well with the frequently used method as described by von Clauss.[26] Total homocysteine was measured as a fluorescent derivate using HPLC according to Araki and Sako,[27] as modified by Ubbink.[28] White blood cell count (leucocytes) and haematocrit were quantified by a Coulter counter (Coulter Electronics, Inc, USA). Height and weight were measured and the body mass index (kg/m^2) was calculated. Body fat distribution was assessed by the ratio of waist and hip circumferences.

Age- and gender-adjusted odds ratios with 95% confidence intervals were calculated using a logistic regression model with the presence of peripheral arterial disease (PAD) as the dependent variable, for a threshold value of the AAI of both 0.90 and 0.70. Next, multivariate odds ratios with 95% confidence intervals were calculated to assess the independent contribution of individual risk indicators, using the same threshold values for the AAI. To assess the proportion of PAD in the population that may be attributed to a certain risk indicator, the etiological fraction (EF) was calculated, using the formula EF= CF x (RR-1)/RR, where the relative risk (RR) is taken as the odds ratio (OR) of the risk indicator resulting from the multiple logistic regression

analyses, and the case fraction (CF) is the prevalence of the risk indicator in those with PAD (29). Analyses were performed using BMDP software (BMDP Statistical Software, Inc., Los Angeles, USA).

Table 1: General characteristics of 6,450 men and women aged 55 years or over in whom the presence of peripheral arterial disease (PAD) was assessed.

Characteristic		Men (n=2,589)		Women (n=3,861)	
Age (years), mean (SD)*		68.3	(8.4)	70.3	(9.7)
Body mass index (kg/m^2), mean (SD)		25.7	(3.7)	26.7	(4.1)
Waist to hip ratio, mean (SD)		0.96	(0.07)	0.87	(0.09)
Systolic blood pressure (mmHg), mean (SD)		139.0	(22)	140	(23)
Diastolic blood pressure (mmHg), mean (SD)		75.0	(12)	73	(12)
Hypertension (%)†		26.3		32.7	
Intermittent claudication (%)‡		2.1		1.4	
Serum total cholesterol (mmol/l), mean (SD)		6.3	(1.2)	6.8	(1.2)
Serum HDL cholesterol§ (mmol/l), mean (SD)		1.2	(0.3)	1.4	(0.4)
Plasma fibrinogen (g/l), mean (SD)		2.7	(0.7)¶	2.8	(0.7)¶
Leucocytes (10^9/l), mean (SD)		6.8	(1.9)	6.6	(2.1)
Haematocrit (l/l), mean (SD)		0.43	(0.04)	0.40	(0.04)
Total homocysteine (µmol/l), mean (SD)		15.7	(4.3)#	14.5	(4.4)#
Smoking (%)	Current	24.2		17.3	
	Former	59.3		27.8	
Alcohol intake (gr/day), mean (SD)		16.5	(18.7)	6.1	(10.1)
Diabetes mellitus (%)		7.6		8.5	

* SD: standard deviation.
† defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.
‡ according to the criteria of the WHO/ Rose-questionnaire.
§ HDL cholesterol: high density lipoprotein cholesterol.
¶ data available of the first 1,000 men, and of the first 1,700 women of the Rotterdam Study.
# data available of a random sample of 630 men and women participating in the Rotterdam Study.

Results

General characteristics of the study population are given in Table 1. PAD, defined as an AAI <0.90, was present in 19.1% (95% confidence interval (CI) 18.1-20.0) of all participants. Severe PAD, defined as an AAI <0.70, was present in 8.1% (95% CI 7.4-8.7) of all participants. After adjusting for age no major differences in the prevalences

between men and women were observed. A clear increase in the prevalence of PAD with age was observed for both threshold values of the AAI (Figure 1).

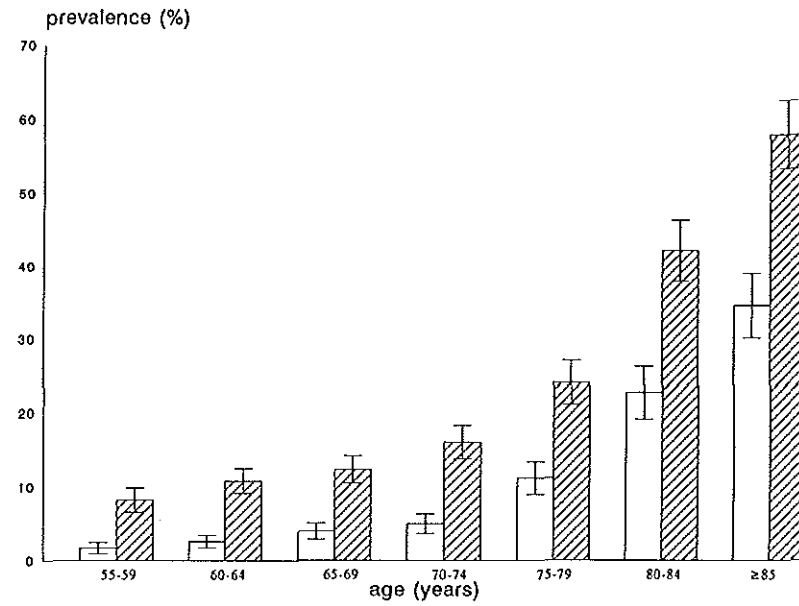

Figure 1. The age-specific prevalence of peripheral arterial disease (PAD) assessed by means of the ankle-arm systolic blood pressure index (AAI), using a threshold value <0.70 (white bars), or using a threshold value <0.90 (shaded bars).

The age- and gender-adjusted odds ratios, and the multivariate odds ratios (with 95% CI) of potential determinants of PAD (defined as an AAI <0.90) and of severe PAD (defined as an AAI <0.70) are shown in Tables 2 and 3, respectively. Only determinants which showed an association with PAD are shown in this table.

Determinants with a strong positive association with PAD were age, fibrinogen level, current smoking of cigarettes, systolic blood pressure, and diabetes mellitus (Table 2). After adjustment for smoking the association between fibrinogen level and PAD decreased slightly, but remained strong. Weaker, and in part statistically non-significant associations with PAD were found for total cholesterol level, leucocyte count, total homocysteine level, and alcohol intake of more than 20 grams a day. There was a clear inverse relation with HDL cholesterol level (Table 2). All other investigated determinants in this study did not show a clear association with PAD. Similar results for PAD with a threshold value of AAI <0.70 were found (Table 3), and separate analyses

for men and women did not reveal differences in risk factors for a threshold value of either 0.90 or 0.70.

Table 2: Potential determinants of peripheral arterial disease (PAD*): age- and gender-adjusted and multivariate odds ratios in 6,450 men and women aged 55 years or over†.

Determinant		Odds ratio (95% confidence interval) of PAD	
		Age- and gender adjusted	Multivariate
Age ≥75 years		1.22 (0.96-1.55)	1.74 (0.97-3.11)
Systolic blood pressure (per 10 mmHg)		1.18 (1.15-1.22)	1.30 (1.18-1.44)
Hypertension‡		1.77 (1.53-2.06)	1.12 (0.91-1.39)
Serum total cholesterol (mmol/l)		1.13 (1.07-1.20)	1.19 (1.05-1.36)
Serum HDL cholesterol (mmol/l)§		0.65 (0.53-0.80)	0.58 (0.35-0.99)
Plasma fibrinogen (g/l)¶		1.49 (1.29-1.72)	1.46 (1.10-1.93)
Leucocytes (10^9/l)		1.10 (1.06-1.14)	1.03 (0.94-1.13)
Total homocysteine (μmol/l)#		1.03 (0.97-1.09)	1.03 (0.96-1.11)
Smoking	Current	2.84 (2.34-3.44)	2.69 (1.67-4.33)
	Former	1.14 (0.96-1.36)	1.15 (0.75-1.78)
Alcohol intake	≥20 gr/day	1.24 (0.99-1.55)	1.00 (0.87-1.42)
Diabetes mellitus		2.00 (1.58-2.53)	1.89 (1.02-3.50)

* defined as an ankle-arm systolic blood pressure index (AAI)<0.90, compared to subjects with an AAI ≥0.90.
† Only determinants which showed a statistically significant association with PAD are shown in the table.
‡ defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.
§ HDL cholesterol: high density lipoprotein cholesterol.
¶ data available of the first 1,000 men, and of the first 1,700 women of the Rotterdam Study.
# data available of a random sample of 630 men and women participating in the Rotterdam Study.

In Table 4 the estimated proportion of PAD that may be attributed to the risk factors resulting from the analyses are given. Of the irreversible risk factors for PAD assessed in this study, age over 75 years explains 11% of the occurrence of PAD. Reversible risk factors for PAD, such as hypertension, serum total cholesterol level of 6.2 mmol/l or over, serum HDL cholesterol level lower than 0.9 mmol/l, current and former smoking, plasma fibrinogen level of 3.5 g/l or over, and diabetes mellitus contribute to 45% of all cases of PAD. In total, 56% of the occurrence of PAD in this

study is accounted for, which leaves 44% of the etiology of PAD unexplained by the determinants considered in this study.

Table 3: Potential determinants of severe peripheral arterial disease (PAD*): age- and gender-adjusted and multivariate odds ratios in 6,450 men and women aged 55 years or over†.

Determinant		Odds ratio (95% confidence interval) of PAD	
		Age- and gender adjusted	Multivariate
Age ≥75 years		1.46 (1.03-2.07)	1.08 (1.01-1.15)
Systolic blood pressure (per 10 mmHg)		1.18 (1.13-1.23)	1.34 (1.18-1.53)
Hypertension‡		1.71 (1.41-2.07)	1.30 (0.75-2.24)
Serum total cholesterol (mmol/l)		1.15 (1.06-1.24)	1.19 (0.98-1.45)
Serum HDL cholesterol (mmol/l)§		0.59 (0.44-0.80)	0.39 (0.18-0.87)
Plasma fibrinogen (g/l)¶		1.63 (1.35-1.97)	1.34 (0.90-2.01)
Leucocytes (10^9/l)		1.05 (1.01-1.10)	1.04 (0.91-1.18)
Total homocysteine (μmol/l)#		1.04 (0.96-1.13)	1.05 (0.92-1.18)
Smoking	Current	3.35 (2.53-4.44)	1.66 (0.79-3.50)
	Former	1.28 (0.99-1.66)	1.20 (0.63-2.30)
Alcohol intake	≥20 gr/day	1.32 (0.93-1.87)	1.02 (0.83-1.77)
Diabetes mellitus		2.44 (1.82-3.28)	2.73 (1.26-5.91)

* defined as an ankle-arm systolic blood pressure index (AAI)<0.70, compared to subjects with an AAI ≥0.70.
† Only determinants which showed a statistically significant association with severe PAD are shown in the table.
‡ defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.
§ HDL cholesterol: high density lipoprotein cholesterol.
¶ data available of the first 1,000 men, and of the first 1,700 women of the Rotterdam Study.
# data available of a random sample of 630 men and women participating in the Rotterdam Study.

Discussion

In our large population-based study we were able to assess many possible determinants of PAD. Using either a threshold value of 0.90 or 0.70 to define PAD we observed a strong association with fibrinogen level, HDL cholesterol level, current smoking, diabetes mellitus, and systolic blood pressure. Similar estimates were observed in men

and women. Risk factors included in our study explained almost 60% of the occurrence of PAD.

Our findings of a positive association between age, smoking, fibrinogen level, and diabetes mellitus with PAD are consistent with previous findings.[5-7,12,30-38] While most previous studies assessed these associations separately, in this study we were able to assess the association between PAD and many determinants simultaneously. The positive association between fibrinogen level and PAD, even after adjustment for smoking, supports earlier findings of the Edinburgh Artery Study that fibrinogen level has an independent role in atherogenesis in relation to PAD.[38] The positive associations of systolic blood pressure, total cholesterol level, leucocyte count, alcohol intake, and the inverse association of HDL cholesterol with PAD are also in accordance with other studies.[5,10,12,13,31,32,37,39-43] In our study we did not find an association between hyperhomocyst(e)inaemia and PAD, in contrast to several earlier studies,[44-47] but this may be attributable to the older population (mean age 67.8 years) included in our study.

Table 4: Case fraction and etiological fraction of different risk factors of peripheral arterial disease (PAD).

Risk indicator	Case fraction* (%)	Etiological fraction† (%)
Age ≥75 years	25.8	11.0
Hypertension‡	42.1	4.5
Serum total cholesterol ≥ 6.2 mmol/l§	57.5	6.7
Serum HDL cholesterol < 0.9 mmol/l§	14.3	2.5
Plasma fibrinogen¶ ≥ 3.5 g/l	11.7	3.7
Smoking Current	28.9	18.1
Former	32.1	4.2
Diabetes mellitus	11.4	5.4

* Case fraction: the prevalence of the risk indicator among subjects with PAD.
† Etiological fraction: the proportion of PAD that may be attributed to the risk factor.
‡ defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.
§ according to the guidelines of the National Cholesterol Education Program (NCEP) Expert Panel (JAMA 1993;269:3015-23).
¶ data available of the first 1,000 men, and of the first 1,700 women of the Rotterdam Study.

We showed that the proportion of PAD that may be attributed to the determinants included in our study is 56%. This finding suggests that research is needed to identify additional factors involved in the etiology of PAD. Alternatively, however, the 44% of the presence of PAD not accounted for could be explained in part by limitations in the assessment of the presence and degree of PAD.

The ankle-arm systolic blood pressure index (AAI) was used as a non-invasive measure of PAD. A threshold value of 0.90 which we used is up to 95% sensitive and about 100% specific in detecting angiogram-positive disease [48] and is related to the severity of the disease.[49] Furthermore, Fowkes et al found a close relationship between the AAI and the results of duplex scanning of the major arteries of the leg.[50] As in most studies, we used a single measurement of the AAI to define PAD. Taking the mean of consecutive measurements would have strengthened the observed associations.

We conclude that a range of cardiovascular risk factors such as hypertension, cholesterol, smoking, fibrinogen level, and diabetes mellitus account for 60% of all cases of PAD. More research is needed to further disclose the etiology of PAD. Our results suggest that preventive management for PAD should be directed at systolic blood pressure, fibrinogen level, total and HDL cholesterol level, smoking, and diabetes mellitus.

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Chapter 4

Glucose as a Risk Factor for the Progression of Peripheral Arterial Disease

Manuscript based on chapter 4:

Meijer WT, Stolk RP, Hoes AW, Hofman A, Pols HAP, Grobbee DE. Glucose, but not insulin, as a risk factor for the progression of peripheral arterial disease in the elderly. The Rotterdam Study (submitted).

Introduction

Diabetes mellitus and raised glucose levels are well known risk factors for cardiovascular disease.[1,2] Moreover, subjects with a history of cardiovascular disease are usually insulin resistant.[3] Insulin resistance is associated with a cluster of cardiovascular risk factors (including hyperglycemia, dyslipidemia, obesity, and hypertension), which has been referred to as 'Syndrome X' or the 'insulin resistance syndrome'.[4,5] Together, these findings suggest that an increased insulin level may also be a risk factor for cardiovascular disease, but several population-based follow-up studies have failed to prove this.[6] To further investigate the role of glucose and insulin as cardiovascular risk factors, we prospectively studied the association between these factors and the progression or incidence of peripheral arterial disease (PAD) in 965 participants of the population-based Rotterdam Study.

Methods

The Rotterdam Study is a population-based cohort study of determinants of chronic disabling diseases in the elderly. All inhabitants of a suburb of Rotterdam, aged 55 years and over (including those living in institutions) were invited to participate. An outline of the study and its objectives has been published previously.[7] The baseline examination was conducted from 1990 to 1993, and included 7,983 subjects (response rate 78%). Participants were interviewed at home by trained research assistants, using a computerized questionnaire, which included an assessment of current medication use. Subsequently, the participants visited the research center for several measurements, including an oral glucose tolerance test. From all subjects informed consent was obtained and the study was approved by the medical ethics committee of Erasmus University Medical School.

During the first follow-up examination of the Rotterdam Study in 1993-1994, a sample of participants of the Rotterdam Study was invited for an additional diabetes study, which included an assessment of PAD. The participants were selected from those aged 55 to 75 years at the baseline examination. The selection consisted of a random sample of about 200 subjects with diabetes mellitus, 400 with hyperinsulinemia (post-load insulin/glucose ratio in the upper quintile), and 600 subjects with a normal glucose tolerance. Equal numbers of men and women were selected, whereas subjects with probable dementia were excluded. In total, 1,107 subjects participated in the diabetes study (response rate 90%). In 142 subjects the ankle-arm index (AAI) was not measured

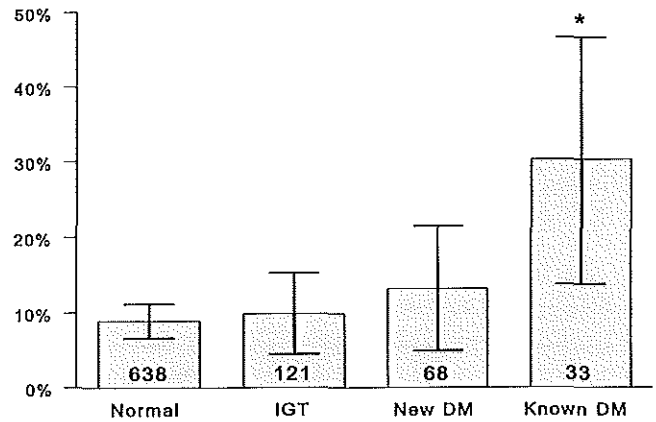
at baseline or at the follow-up examination, due to technical problems of the equipment. The results presented in this article are based on data from the remaining 965 participants.

At the baseline examination the participants visited the research center throughout the day. Blood was drawn by venepuncture and subjects not using antidiabetes medication (tablets or insulin) received a glucose drink of 75 grams of glucose. Two hours later a second blood sample was obtained. Insulin was measured by radioimmunoassay (Medgenix diagnostics, Brussels, Belgium) in the post-load sample only. Glucose levels were measured in both samples by the glucose hexokinase method. Also the fructosamine level was measured. Diabetes mellitus was defined as the use of antidiabetes medication or a random or post-load glucose level greater than 11.0 mmol/l.[8] Subjects with increased glucose levels and not using antidiabetes medication were categorized as newly diagnosed diabetes. Those with a post-load glucose between 7.8 and 11.1 mmol/l were considered to have impaired glucose tolerance.[9]

Both at baseline and during follow-up visit blood pressure was measured with a random-zero sphygmomanometer, and the mean of two measurements was used in the analyses. Hypertension was defined as a systolic blood pressure of 160 mmHg or over and/or a diastolic blood pressure of 95 mmHg or over and/or the use of antihypertensive medication. Body mass index was calculated as weight divided by the square of height (kg/m^2).

The ankle-arm systolic blood pressure index (AAI), the ratio of systolic blood pressure in the ankle over the systolic blood pressure in the arm, was used as measure of PAD.[10] Ankle systolic blood pressure was measured at the posterior tibial artery with a Doppler ultrasound 8 MHz transducer (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, UK) while the subject was in supine position. The lowest AAI in either leg was used in the analyses. PAD was defined as an AAI lower than 0.90.[10]

The associations between baseline glucose, insulin and diabetes mellitus with the change in AAI was assessed by linear regression analyses, with the change in AAI per year as the dependent variable. To adjust for possible confounding factors, notably age, antihypertensive medication and body mass index, multiple linear regression analysis was performed. Using Cox' proportional hazard analyses, likelihood ratios (as an approximation of relative risks) with the measure of glucose metabolism as the independent and the incidence of PAD as dependent variable were estimated, again adjusting for possible confounding factors.



Figures in bar represent number of subjects in each category, error bars indicate the 95% confidence interval.

*p <0.05, compared to normal glucose tolerance.

Normal	= normal glucose tolerance.
IGT	= impaired glucose tolerance: random or post-load glucose >8 mmol/l.
New DM	= newly diagnosed diabetes mellitus.
Known DM	= known diabetes mellitus.

Figure 1. The cumulative incidence of peripheral arterial disease (PAD) by categories of glucose tolerance at baseline.

Results

The baseline characteristics of the study population are given in Table 1. The average period between the two measurements of the AAI was 2.1 years (range 0.6-5.1). During this period the average decrease of the AAI was 0.0086 (SD 0.24), whereas the cumulative incidence of PAD was 10.3% (95% CI: 8.2-12.2). These estimates were similar in men and women. In subjects with diabetes mellitus at baseline the incidence of PAD was 18.8% (95% CI: 10.9-26.3), whereas in those without diabetes the incidence was 9.2% (95% CI: 7.0-11.1).

Baseline glucose and fructosamine levels, and the presence of diabetes mellitus, were associated with a decline of AAI, whereas baseline insulin levels showed no association (Table 2). This pattern was even more pronounced for incident PAD within

the mean follow-up period of 2.1 years (Table 3). Figure 1 gives the cumulative incidence of PAD by categories of glucose intolerance at baseline. The cumulative incidence was highest in subjects with known diabetes mellitus. All associations were essentially the same in men and women, and did not change after further adjustment for baseline AAI, use of antihypertensive medication, total cholesterol, HDL-cholesterol, waist-hip ratio or body mass index.

Table 1: General characteristics of 965 men and women aged 55 years or over in whom the presence of peripheral arterial disease (PAD) was assessed.

Age (years), mean (SD)*	64.5	(5.3)
Men (%)	49.7	
Body mass index (kg/m^2), mean (SD)	26.5	(3.4)
Waist to hip ratio, mean (SD)	0.91	(0.09)
Random serum glucose level (mmol/l), mean (SD)	7.1	(2.8)
Fructosamine level (µmol/l), mean (SD)	312	(52.3)
Post-load insulin level (mU/l), mean (SD)	69.4	(54.5)
Diabetes mellitus (%)†	12.4	
Serum total cholesterol level (mmol/l), mean (SD)	6.7	(1.1)
Serum HDL cholesterol level (mmol/l), mean (SD)	1.3	(0.4)
Systolic blood pressure (mmHg), mean (SD)	137	(20.9)
Diastolic blood pressure (mmHg), mean (SD)	74.5	(11)
Hypertension (%)‡	26.3	
Ankle-arm systolic blood pressure index, mean (SD)	1.12	(0.17)
Peripheral arterial disease (%)§	10.2	

* SD: standard deviation.
† defined as use of antidiabetes medication, or random glucose level of 11.1 mmol/l or over, or a post-load glucose level of 11.1 mmol/l or over.
‡ defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.
§ defined as an ankle-arm systolic blood pressure index (AAI) <0.90.

Table 2: Associations between glucose metabolism at baseline and change of ankle-arm systolic blood pressure index (per year).

		Coefficient*	95% confidence interval		*p*-value
Glucose	(per 2.8 mmol/l)	-0.014	-0.023	-0.006	<0.01
Fructosamine	(per 52.3 µmol/l)	-0.013	-0.022	-0.004	<0.01
Insulin	(per 54.5 mU/l)	-0.01	-0.016	0.002	0.11
Diabetes mellitus†		-0.025	-0.050	0.0009	0.06

* age- and gender-adjusted coefficients of linear regression, for continuous variables per standard deviation.
† defined as use of antidiabetes medication, or random glucose level of 11.1 mmol/l or over, or a post- load glucose level of 11.1 mmol/l or over.

Table 3: Associations between glucose metabolism at baseline and the incidence of peripheral arterial disease (PAD).

		Coefficient*	95% confidence interval	*p*-value
Glucose	(per 2.8 mmol/l)	1.24	1.06 - 1.44	<0.01
Fructosamine	(per 52.3 µmol/l)	1.35	1.12 - 1.64	<0.01
Insulin	(per 54.5 mU/l)	0.98	0.78 - 1.24	0.88
Diabetes mellitus†		1.94	1.15 - 3.28	0.01

* age- and gender-adjusted coefficients of linear regression, for continuous variables per standard deviation.
† defined as use of antidiabetes medication, or random glucose level of 11.1 mmol/l or over, or a post- load glucose level of 11.1 mmol/l or over.

Discussion

In this population-based follow-up study serum glucose levels and the presence of diabetes mellitus were associated with progression of PAD, whereas insulin levels were not.

A limitation of the Rotterdam Study is the use of a non-fasting blood sample during the baseline examinations. Therefore, the diagnostic limit of the baseline glucose level of the oral glucose tolerance test (OGTT) was set at 11.1 mmol/l instead of 7.8 mmol/l used by the WHO.[8] This leads to an underestimation of the prevalence of diabetes. However, the number of false-positive diagnoses of diabetes mellitus is reduced by this approach. Insulin was measured two hours after the oral glucose load. We reported previously that these levels are similar to the fasting post-load levels.[11] In subjects without diabetes mellitus the post-load insulin level provides a good measure of insulin resistance.[12]

In epidemiologic studies the AAI is commonly used to assess the degree of PAD.[13,14] It has been shown that the AAI is strongly associated with both the presence of atherosclerosis at other sites of the arterial system, and future occurrence of cardiovascular events.[15] Although mediasclerosis is more prevalent in subjects with diabetes mellitus than in the general population and invalidates the measurement of the ankle blood pressure, the AAI has been recommended as a measure of atherosclerosis in subjects with diabetes mellitus.[16] Because we only measured the AAI once at every occasion, our analyses will have been influenced by 'regression to the mean' which leads to decreased follow-up values in those subjects with high values at baseline. As a result, the reported associations are likely to be underestimations of the real relationships.

Cross-sectional studies determining the associations of glucose and insulin with peripheral atherosclerosis, using carotid intima media thickness [17] and physical signs of PAD,[18] also found associations with glucose, and not with insulin. The association between raised glucose levels and progression of atherosclerosis or the development of cardiovascular disease is well established, both in subjects with and without diabetes mellitus,[1,2,19-21] and is confirmed in our study. A publication from the Rancho Bernardo Study, however, only showed an association between glycosylated hemoglobin and cardiovascular mortality, but not for glucose levels.[22] This supports the notion that the glycosylation of proteins and other macromolecules (advanced glycosylation end-products) play a central role in the pathogenesis of diabetes vascular complications.[23,24] In a commentary, one of the investigators of the Rancho Bernardo Study suggested that the increased cardiovascular risk of diabetes is mainly due to the presence of other

cardiovascular risk factors (dyslipidemia, hypertension) and not to increased glucose levels.[25] The associations between glucose and change in AAI in the present study, however, were independent of obesity, dyslipidemia, and hypertension.

The role of insulin as risk factor for the progression of PAD is not well determined. Laboratory studies have shown that insulin may promote atherosclerosis either by a direct anabolic effect on the arterial wall [26,27] or by influencing cholesterol metabolism.[28] In cross-sectional studies associations have been found between increased insulin levels and degree of atherosclerosis, measured by carotid artery wall thickness,[29,30] and distensibility of the aorta.[31] However, these reported associations were rather weak, whereas other investigators found no association at all.[32,33] Moreover, in population-based studies both higher, equal, and lower incidences of cardiovascular diseases in subjects with hyperinsulinemia have been reported.[6] Interestingly, an increased cardiovascular risk was found in the earlier studies, whereas more recent studies did not find an association.[6] The lack of association between hyperinsulinemia and the progression of PAD observed in our study supports the findings of the more recent studies.

Symptomatic cardiovascular disease is the result of a thrombotic occlusion of an atherosclerotic artery. Raised insulin levels in subjects with symptomatic cardiovascular disease,[3,34] combined with the lack of association between insulin and the progression of PAD found in the present study, suggest an association between insulin and increased thrombotic activity. Impaired fibrinolysis may be a stronger determinant of an occlusion than increased hemostasis.[35] Indeed it has been shown that insulin is positively associated with plasminogen activator inhibitor 1 (PAI1).[36] In addition, insulin impairs vasoconstrictive responses, which increases intra-capillary pressure.[37]

In conclusion, the results of this study indicate that insulin does not play a direct role in the progression of PAD but confirm the importance of elevated serum glucose as a risk factor for atherosclerotic disease.

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Chapter 5

Incidence of Peripheral Arterial Disease

Manuscript based on chapter 5:

Meijer WT, Hunink MGM, Hofman A, Grobbee DE, Hoes AW. Incidence of peripheral arterial disease in the elderly. The Rotterdam Study (submitted).

Introduction

Atherosclerotic occlusion of the arterial system of the lower limbs, generally known as peripheral arterial disease (PAD), is asymptomatic in early stages, and when it becomes symptomatic presents itself as intermittent claudication: ischemic pain in the calf of the leg, induced by walking and relieved by standing still.[1-3] PAD is a relatively common disorder in the elderly, and is a manifestation of generalized atherosclerosis. In both patients with and without symptoms of PAD a reduced life expectancy is observed, which is mainly attributable to cardiovascular disease.[4-6]

Several large, population-based studies have shown that the prevalence of PAD is high in the elderly and clearly increases with advancing age.[7-12] Although several studies on incidence rates of intermittent claudication as determined by the WHO/Rose questionnaire are available, population-based data on the age- and sex-specific incidence rates of PAD assessed by measuring the ankle-arm systolic blood pressure index (AAI) are virtually lacking.

The purpose of this study was to assess the age- and sex-specific incidence rates of PAD and intermittent claudication and determinants of incident PAD in a large population-based cohort of older subjects.

Methods

This study is part of the Rotterdam Study, a prospective follow-up study designed to investigate determinants of the occurrence and progression of chronic diseases in the elderly. The rationale and design of the study have been described previously.[13]

All individuals aged 55 years and over, living in the suburb of Ommoord in Rotterdam, the Netherlands (a total of 10,275 subjects), were invited to participate. Baseline measurements (1990-1993) comprised an extensive interview at the participant's home and two visits to the research center. The overall response rate was 78% (n=7,983; 3,105 men and 4,878 women). Of these, 879 lived in nursing homes. Due to several reasons, such as refusal and logistic problems, the AAI was not determined in 1,533 participants. Also, 39 participants were excluded because they had an AAI greater than 1.50, which usually reflects arterial rigidity preventing arterial compression, leading to spuriously high ankle blood pressure values. Thus, PAD was assessed in 6,411 participants at baseline.

Follow-up measurements took place between April 1997 until May 1999 and comprised an extensive interview at the participant's home and two visits to the

research center. At baseline 1,222 individuals (19%) had an ankle-arm index below 0.90, and were therefore excluded. This resulted in a cohort of 5,189 individuals (41% men, 59% women) that was followed to assess the incidence of PAD. At the follow-up examination the AAI was measured in 2,917 of these subjects (56.2%). In total 800 (15.4%) had died before the follow-up measurement and 697 (13.4%) refused to visit the research center, 50 (1.0%) could not be reached and in 168 (3.2%) the AAI was not determined due to logistic reasons. In addition, in 557 subjects (10.7%) the visit to the research center was planned after the time of our analyses.

At baseline, responses to the WHO/Rose questionnaire [14] were available for 7,715 participants. Of those, we excluded 124 persons who reported symptoms of intermittent claudication at baseline (2%), leaving 7,591 individuals (39% men, 61% women) who were followed to determine the development of intermittent claudication. Responses to the WHO/Rose questionnaire at the follow-up assessment were available for 3,836 participants (50.5%). Reasons for non-availability were: death before the follow-up assessment (n=1,766 (23.3%)), refusal of the home interview (n=778 (10.2%)); 79 (1.0%) could not be reached, in 460 (6.1%) the home interview was incomplete or not performed due to logistic reasons, and in 672 (8.9%) the interview was planned after our analyses were completed.

Blood pressure was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer at the right brachial artery in sitting position. The ankle blood pressure was assessed by measuring the systolic blood pressure level of the posterior tibial artery at both the left and right leg using a 8 MHz continuous wave Doppler probe (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, UK) and a random-zero sphygmomanometer.[15-18] For each leg a single blood pressure reading was taken with the subject in supine position.[19] The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm (ankle-arm index) was calculated for each leg. The lowest ankle-arm index (AAI) in either leg was used in the analysis.[7] In agreement with the approach followed by Fowkes et al [7] and by Schroll and Munck,[20] PAD was considered present when the AAI was lower than 0.90 at at least one side, a threshold value used in most studies.[7,9,10,20,21]

Established cardiovascular risk factors were recorded for all participants.[13] Hypertension was defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.[22] Diabetes mellitus was defined as the current use of antidiabetic drugs or a random or post-load serum glucose level greater than 11.0 mmol/l, after an oral glucose tolerance test.[23,24] Subjects were categorized in groups of current smokers, former smokers, and those who never smoked. Total alcohol intake

was calculated from beverage specific information obtained by a semi-quantitative food frequency questionnaire. One drink was approximately equivalent to 10 grams of alcohol. A venipuncture was performed, applying minimal stasis, using a 21 gauge butterfly needle. Samples were collected into siliconized Vacutainer tubes containing 3.8% trisodium citrate and centrifuged for 10 minutes at 1,600 g at 4°C. Plasma was separated, subsequently centrifuged for 10 minutes at 10,000 g at 4°C and stored at -80°C before assay. Serum total cholesterol was determined by an automated enzymatic procedure.[25] Serum high density lipoprotein (HDL) cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium,[26] with a minor modification as described by Grove.[27] Plasma fibrinogen level was measured as derived fibrinogen of the prothrombin time assay using Tromborel S as reagent on an Automated Coagulation Laboratory (ACL 300, Instrumentation Laboratory, IJsselstein, The Netherlands).[28] This method correlates well with the frequently used method as described by von Clauss.[29] Height and weight were measured and the body mass index (kg/m^2) was calculated.

Age- and sex-specific incidence rates of peripheral arterial disease (PAD) and intermittent claudication were estimated per 5 year age category by means of the person-years method (number of incident cases divided by the number of person-years, i.e. the sum of each participants's contribution of follow-up time per age-group). Poisson standard errors and 95% confidence intervals (95% CI) of the incidence estimates were calculated. Multivariate relative risks with 95% confidence intervals were calculated to assess the independent contribution of individual risk factors to the risk for PAD using Cox' proportional hazards model with the presence of incident PAD as the dependent variable. All analyses were performed using SPSS software (SPSS for Windows 7.5, SPSS Inc., Chicago, USA).

Results

During the mean follow-up period of 6.5 years (range 5.1-9.5) 363 persons developed PAD. The overall incidence rate of PAD was 22.7 per 1,000 person years (95% confidence interval (95% CI): 20.4-25.1) and was very similar in men (22.9 per 1,000 person years) and women (22.5 per 1,000 person years). In both men and women, an increase in the incidence of PAD with age was observed, ranging from 9.9 per 1,000 person years in the age category 55 to 59 years to 52.8 per 1,000 person years in the age category 80 years or over in men, and from 15.8 per 1,000 person years to 51.5 per 1,000 person years in the corresponding age categories in women (Figure 1).

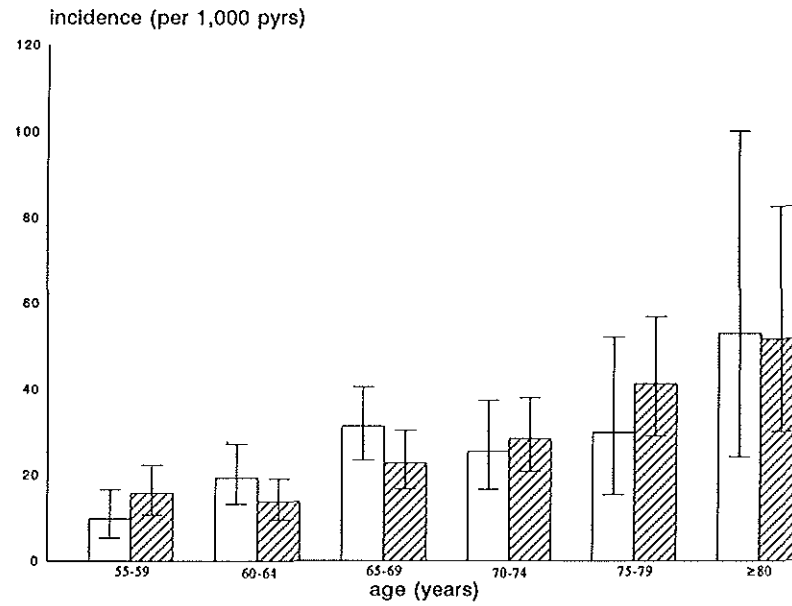

Figure 1. The age- and sex-specific incidence rates of peripheral arterial disease (and 95% CI) according to age, for men (white bars) and women (shaded bars).

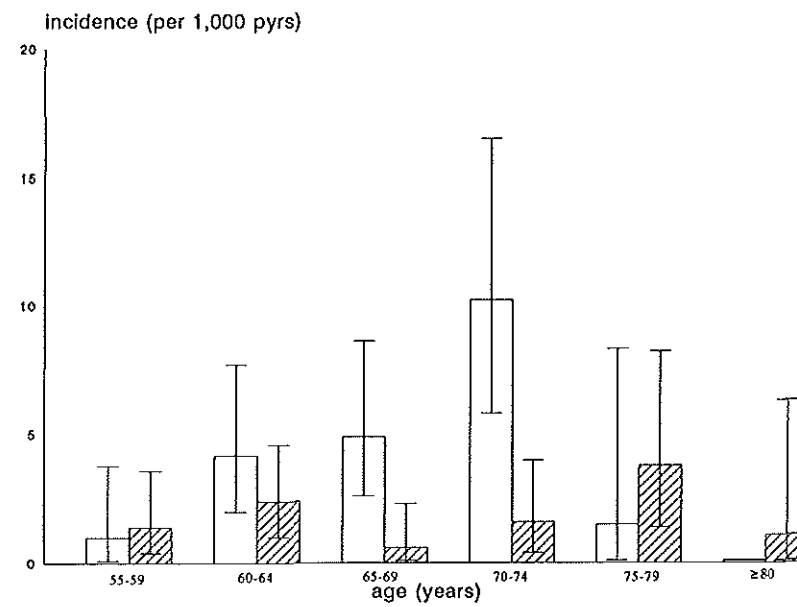

Figure 2. The age- and sex-specific incidence rates of intermittent claudication (and 95% CI) according to age, for men (white bars) and women (shaded bars).

The incidence rate of intermittent claudication was 2.8 per 1,000 person years (95% confidence interval (95% CI): 2.2-3.6); 4.4 per 1,000 person years in men (95% CI: 3.2-6.0), and 1.7 per 1,000 person years in women (95% CI: 1.1-2.6). An increase in the incidence of intermittent claudication with age was observed, notably in men ranging from 1.0 per 1,000 person years in the age category 55 to 59 years to 10.2 per 1,000 person years in the age category 70 to 74 years. Lower incidence rates were observed after the age of 75 years in men and after the age of 80 years in women (Figure 2).

Of the 363 incident cases of PAD, 3.9% reported symptoms of intermittent claudication (4.7% in men, 3.3% in women). Symptoms of intermittent claudication at the end of follow-up were reported by 4.7% of those with PAD and no complaints of intermittent claudication at baseline (9.6% in men, 2.4% in women). Compared to participants with an AAI ≥0.90 and no complaints of intermittent claudication at baseline, participants with asymptomatic PAD (AAI <0.90 and no intermittent claudication at baseline) experienced a 4 fold risk of developing intermittent claudication.

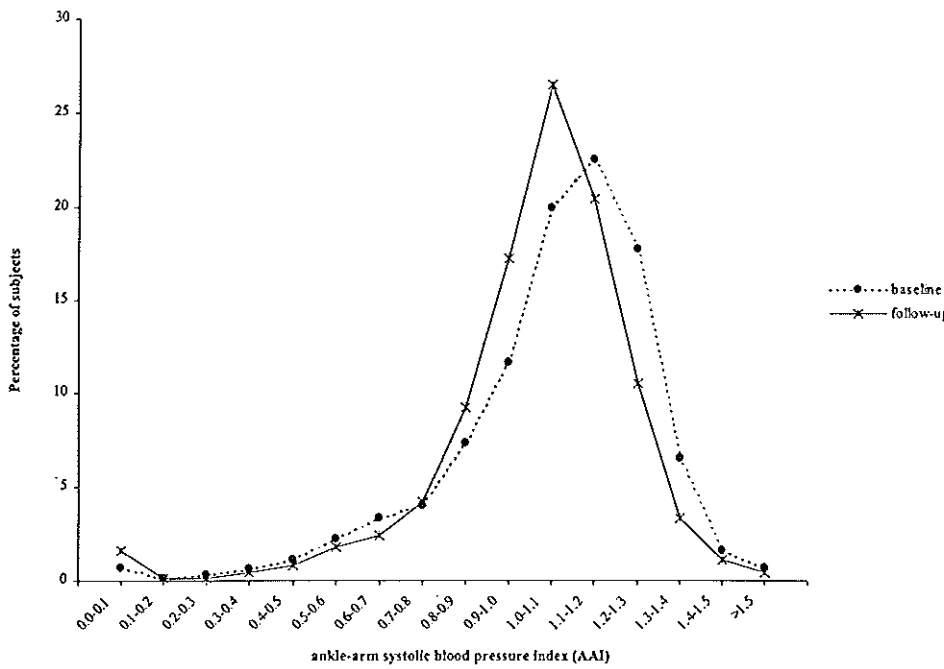

Figure 3. The distribution of the ankle-arm systolic blood pressure index in subjects aged 55 years or older at baseline (1990-1993) and at follow-up (1997-1999).

Both at baseline and follow-up the mean AAI decreased with advancing age, and the distribution of AAI values was skewed to the left (Figure 3). During the mean follow-up period of 6.5 years, the average decrease of the AAI was 0.093 (SD 0.23); 0.119 (SD 0.22) in men and 0.076 (SD 0.23) in women.

In Table 1 the independent contribution of individual risk factors to the risk for incident PAD is shown. Strong and independent predictors were age ≥ 70 years (relative risk (RR) 1.6; 95% confidence interval (CI) 1.2-2.0), male gender (RR 1.5; 95% CI 1.1-1.9), smoking (RR 1.5; 95% CI 1.1-2.0), diabetes mellitus (RR 2.7; 95% CI 1.6-4.6), fibrinogen level ≥3.5 g/l (RR 1.9; 1.4-2.7), and systolic blood pressure (RR 1.1; 95% CI 1.0-1.2).

Table 1: Predictors of incident PAD (AAI<0.90) during a mean follow-up of 6.5 years. Results from multiple regression analyses.

Risk factor		Relative risk	95% Confidence Interval
Age (years)	≥ 70 vs. <70	1.6	1.2 - 2.0
Gender	male vs. female	1.5	1.1 - 2.0
Body mass index	≥ 25 kg/m^2	0.8	0.6 - 1.0
Systolic blood pressure	(per 10 mmHg)	1.1	1.0 - 1.2
Diastolic blood pressure	(per 10 mmHg)	1.0	0.8 - 1.1
Hypertension*		0.9	0.7 - 1.3
Serum total cholesterol	≥ 6.2 mmol/l†	1.2	0.9 - 1.5
Serum HDL‡ cholesterol	< 0.9 mmol/l†	0.9	0.6 - 1.4
Plasma fibrinogen	≥ 3.5 g/l	1.9	1.4 - 2.7
Alcohol intake	≥ 20 gr/day	0.8	0.6 - 1.1
Smoking	current vs. never	1.5	1.1 - 2.0
Diabetes mellitus		2.7	1.6 - 4.6

* defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.

† according to the guidelines of the National Cholesterol Education Program (NCEP) Expert Panel (JAMA 1993;269:3015-23).

‡ HDL cholesterol: high density lipoprotein cholesterol.

Only in 16.4% of all participants at follow-up (35% men) the decrease of the AAI was greater or equal to 0.1. Multivariate regression analyses (using the decrease of the AAI ≥ 0.1 against <0.1 as the dependent variable) identified the same determinants as in the analyses including incident PAD as dependent variable, but most associations did not reach conventional levels of statistical significance.

Discussion

During a mean follow-up period of 6.5 years, the incidence of PAD in the elderly was high (22.7 per 1,000 person years), and similar in men and women, whereas the incidence rate of intermittent claudication, 2.8 per 1,000 person years, was relatively low, notably in women (1.7 per 1,000 person years). Both incidences increased with advancing age. Diabetes mellitus, fibrinogen level ≥3.5 g/l, and smoking were strong and independent predictors of future PAD.

To this date, only few studies reported incidence rates on PAD. Most of these studies determined the incidence of intermittent claudication based on the WHO/Rose questionnaire and incidence rates ranged from 3.6 to 15.5 per 1,000 person years.[6,30-33] The latter incidence of intermittent claudication reported by the Edinburgh Artery Study[6] used answers to the Rose questionnaire, mailed responses, or notifications of GPs to assess intermittent claudication. Three studies included male participants only, and their reported incident rates of intermittent claudication are comparable with our findings.[31-33] The figures reported by the Framingham Study [30] are somewhat higher than ours being 3.6 per 1,000 for women (Rotterdam 1.7) and 7.1 per 1,000 for men (Rotterdam 4.4).

Since the vast majority of patients with PAD is asymptomatic, a non-invasive measure such as the AAI is essential to obtain a clear picture of the incidence of PAD in the elderly. To our knowledge, however, this issue was only addressed in one study among 18 general practices in the south of the Netherlands. An overall incidence rate of 9.9 per 1,000 person years was found among subjects with an AAI <0.95 and no intermittent claudication at baseline.[34] The in comparison to our study lower estimates are attributable to the use of different criteria to define PAD, the exclusion of subjects with intermittent claudication, and the younger study population. Their increase of the incidence of PAD with age is consistent with our findings. Our estimated incidence rates could be biased in several ways. In 56% of the cohort members the AAI was remeasured. In particular, the 15% of the non-participants who refused to participate or could not be reached, could have reduced our estimates, assuming that the incidence in

these subjects is higher. However, non-responders (refusal and inaccessability) did not differ appreciably in age, gender or other determinants of PAD from the responders. Secondly, the exact time of the occurrence of PAD in the incident cases is not known. Assuming that PAD occurred halfway between baseline and follow-up measurements (including half of contributed person years (pyrs) of incident cases to the denominators), yielded higher incidence rates (24.5 per 1,000 pyrs (95% CI 22.0-27.1) instead of 22.7 per 1,000 pyrs (95% CI 20.4-25.1)). Finally, we used a single measurement of the AAI at every occasion. Taking the mean of several consecutive measurements, as was the case in the study in the south of the Netherlands,[34] is likely to have reduced the estimates.

Interestingly, women with PAD less often developed symptoms of intermittent claudication (2.4%) during the follow-up period than men with PAD (9.6%). This is consistent with our cross-sectional observations.[12]

The ankle-arm systolic blood pressure index (AAI), was used as a non-invasive measure of asymptomatic PAD. The threshold value of 0.90 we used is up to 95% sensitive and about 100% specific in detecting angiogram-positive disease,[35] and is related to the severity of the disease.[36] Fowkes et al found a close relationship between the AAI and the results of duplex scanning of the major arteries of the leg.[37]

We conclude that the incidence of PAD in the elderly is high whereas the incidence of intermittent claudication is relatively low, and that both incidences increase with advancing age. Life expectancy in patients with PAD is reduced and the incidence of cardiovascular disease is clearly increased,[4,5,9,38-40] also in subjects without intermittent claudication.[7,9] The identification of several indepent risk factors for incident PAD in this study, offers opportunities to prevent the development of PAD.

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Chapter 6

Incidence of Intermittent Claudication in Primary Care

Manuscript based on chapter 6:

Meijer WT, Cost B, Bernsen RMD, Hoes AW. Incidence and management of intermittent claudication in primary care in the Netherlands (submitted).

Introduction

Peripheral arterial disease (PAD) is a relatively common disorder in the elderly, and in a minority of cases this chronic disorder becomes symptomatic as intermittent claudication: pain in the calf of the leg, induced by walking, and relieved by standing still.[1-3]

In the Netherlands and in the UK most patients with intermittent claudication are detected and managed in general practice. Data on the incidence and management of intermittent claudication in primary care are, however, relatively scarce.[4-7]

We studied the incidence of intermittent claudication as presented in primary care in the Netherlands and the subsequent management of these patients by their general practitioner.

Methods

We used data from the Dutch National Survey of Morbidity and Interventions in General Practice, carried out in 1987 and 1988 by the Netherlands Institute of Primary Health Care (NIVEL), in which 161 general practitioners (GPs), with in total 74,153 patients aged 55 years and over, participated.[8] The GPs were divided in four groups. The four groups registered every contact between patients and the practice during a consecutive period of three months. The total registration period lasted from April 1st 1987 to April 1st 1988. A special form was designed to register all contacts including diagnoses, referrrals, and prescriptions. The GPs recorded the clinical problem in diagnostic terms on the registration form. From these forms the morbidity data were coded by trained medically qualified coders according to the International Classification of Primary Care (ICPC).[9] Medication was coded using the Anatomical Therapeutical Chemical (ATC) classification index codes.[10] The registration of morbidity in the National Survey is episode oriented. All new episodes registered with the ICPC-code K92 (intermittent claudication), and information on subsequent management of these patients were studied.

Age- and sex-specific incidence rates of intermittent claudication were estimated per 5 year age-groups by means of the person-years method (number of incident cases divided by the number of person-years, i.e. the sum of each participants's contribution of follow-up time per age-group). Poisson standard errors and 95% confidence intervals (95% CI) of the incidence estimates were calculated. Similarly, overall incidence rates of other cardiovascular disease, acute myocardial infarction (K75), heart failure (K77),

atrial fibrillation (K78), hypertension (K86/87), transient ischaemic attack (K89), and stroke (K90), in the database of Dutch National Survey of Morbidity and Interventions in General Practice, were calculated and compared with the overall incidence of intermittent claudication. All analyses were performed using SPSS software (SPSS for Windows 7.5, SPSS Inc., Chicago, USA).

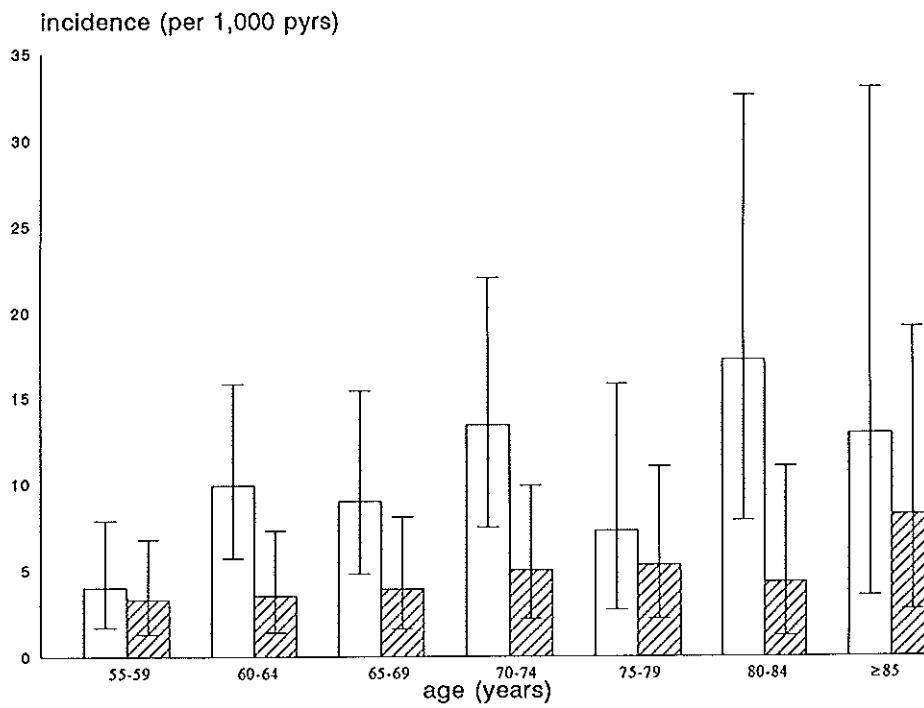

Figure 1. The incidence of intermittent claudication (per 1,000 person years) in primary care in the Netherlands according to age, for men (white bars) and women (shaded bars).

Results

The mean age of the study population was 67.8 years (standard deviation (SD) 9.2); 66.9 years (SD 8.9) in men, and 68.6 years (SD 9.4) in women.

During the study period, comprising 18,286 person years, 117 incident cases of intermittent claudication were diagnosed by the general practitioners; 72 men, and 45 women. The overall incidence of intermittent claudication was 6.4 per 1,000 person years (95% confidence interval (CI): 5.3-7.7); 9.1 (95% CI: 7.1-11.4) in men, and 4.4

(95% CI: 3.2-5.8) in women. The incidence of intermittent claudication increased sharply with age. In men, the incidence increased from 4.0 per 1,000 person years (95% CI: 1.7-7.9) in those aged 55-59 years, to 12.9 per 1,000 person years (95% CI: 3.5-33.0) in those aged over 85 years, and in women in the same age categories from 3.3 per 1,000 person years (95% CI: 1.3-6.8) to 8.2 (95% CI: 2.7-19.1) (Figure 1).

The GPs prescribed medication in about half (47%) of the 117 cases. Most patients (n=25) received peripheral vasodilatators, such as pentoxifylline or isoxsuprine. Aspirin was prescribed in 19 cases (Table 1). Of the 117 incident cases of intermittent claudication 43 (37%) were referred to a specialist, notably to a surgeon (n=21) or an internist (n=6). In 101 cases (86%) the GP gave lifestyle advice, notably pertaining to exercise and cessation of smoking (Table 1).

Table 1: Referral rate and pharmacological and non-pharmacological interventions in 117 patients diagnosed with intermittent claudication in primary care in the Netherlands.

Management	Number (%)	
Referral:		
Any referral	43	(37)
Surgeon	21	(18)
Internist	6	(5)
Cardiologist	4	(3)
Others	12	(10)
Drug prescription:		
Any prescription	55	(47)
Peripheral vasodilatators	25	(21)
Vasoprotectives	2	(2)
Antithrombotic agents	9	(8)
Analgesics	19	(16)
Lifestyle advice	101	(86)

The incidence of intermittent claudication was comparable with the incidence of myocardial infarction and transient ischaemic attack, but lower than the reported incidence of heart failure or hypertension (Figure 2).

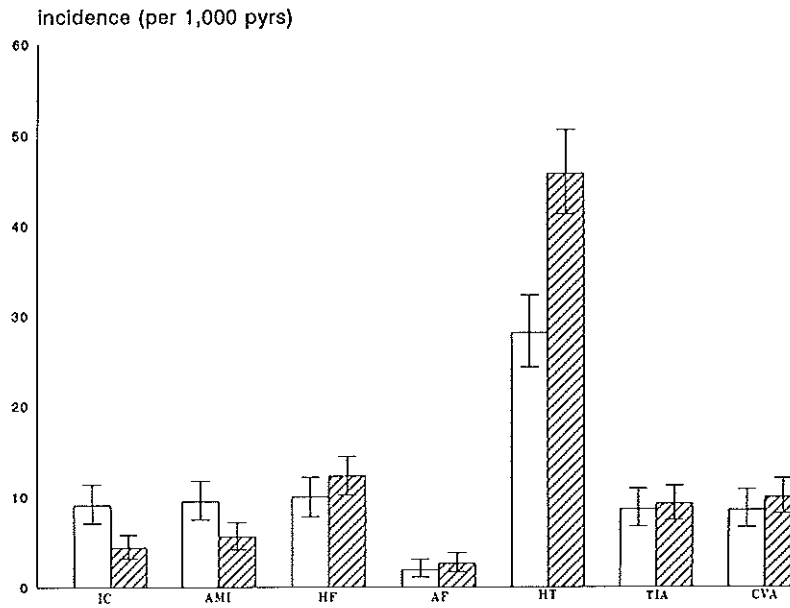

Figure 2. The incidences of various cardiovascular disease and hypertension (per 1,000 person years) in primary care in the Netherlands for men (white bars), and women (shaded bars). IC= intermittent claudication; AMI= acute myocardial infarction; HF= heart failure; AF= atrial fibrillation; HT= hypertension; TIA= transient ischaemic attack; CVA= stroke.

Discussion

The results of this study show that the incidence of intermittent claudication as diagnosed in general practice is comparable with the incidence of myocardial infarction, and increases sharply with age in both men and women. The majority of patients with incident intermittent claudication received lifestyle advice, and 37% was referred to a specialist.

Our specific incidence estimates are comparable to the findings of the Fourth National Study from the UK, and of two other Dutch studies in general practice.[4,5,11] The differences might be due to differences between use of ICD-9, and ICPC-codes, and to differences in study populations, e.g. use of different age strata. An increase in the incidence with advancing age in both men and women is a consistent finding in all studies.

The diagnosis of intermittent claudication in this study was based on the clinical judgement of the GP. The validity of the clinical diagnosis of intermittent claudication as a manifestation of peripheral arterial disease (PAD) in a primary care setting, is based on history taking and physical examination, i.e. determination of absent peripheral pulsations, is difficult. A positive history of intermittent claudication and absent peripheral pulsations both give a high number of false-positive diagnoses.[12,13] Also, the inter-observer variability in the determination of absent peripheral pulsations is large.[14] Although our method closely reflects daily clinical practice, a diagnosis of intermittent claudication or PAD based on history taking and physical examination could lead to underestimation of the incidence rate. Symptomatic (i.e. intermittent claudication) peripheral arterial disease (PAD), as well as asymptomatic PAD is relatively easy to detect by means of the ankle-arm systolic blood pressure index (AAI), a valid non-invasive technique. The AAI can be measured using a simple pocket Doppler device, and is calculated by dividing the systolic blood pressure at the ankle by the systolic arm blood pressure.[3,15,16] Currently, 40% of Dutch GPs have a Doppler device,[17] but the use of this simple technique in day-to-day practice is too limited, the more since measurements of the AAI can be used as a non-invasive marker of asymptomatic atherosclerosis.[18]

Although the data from our study were collected in 1988, the management of intermittent claudication patients by the GP (i.e. lifestyle advice and referral in a minority of cases) closely reflects the current international and Dutch guidelines on management of intermittent claudication.[19-23] The prescription of drugs for intermittent claudication, e.g. peripheral vasodilatators such as pentoxifylline, still remains debatable.[21,24,25] Identification of patients with (usually asymptomatic) PAD can be important in view of the possible benefit of secondary prevention, i.e. improving the cardiovascular risk profile or introducing antiplatelet therapy.[26]

In conclusion, the incidence of intermittent claudication in general practice certainly is not negligible and clearly increases with age in both men and women. Because most PAD patients are asymptomatic (i.e. they do not report symptoms of intermittent claudication) and are missed by history-based diagnosis or physical examination, increased interest in diagnosis of PAD in general practice, in particular by using the ankle-arm systolic blood pressure index, seems necessary.

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Chapter 7

The Ankle-Arm Index as Predictor of Mortality and Morbidity

Manuscript based on chapter 7:

Meijer WT, Hunink MGM, Hofman A, Grobbee DE, Hoes AW. The ankle-arm index predicts mortality and morbidity. The Rotterdam Study (submitted).

Introduction

Atherosclerosis in the lower limb distal to the aortic bifurcation, generally known as peripheral arterial disease (PAD), usually presents itself as intermittent claudication, i.e. 'cramping', 'fatigue' or 'aching' in the calf of the leg, induced by walking, and relieved by standing still. Individuals with PAD, both with and without symptoms of intermittent claudication,[1-3] are at an increased risk of cardiovascular mortality compared to those without.[2,4-7] Information about mortality and morbidity associated with asymptomatic PAD in the general population is relatively scarce, even in older individuals who are known to be at high risk of PAD. Some studies using the ankle-arm systolic blood pressure index (AAI), a non-invasive measure of PAD, suggest that a low AAI is associated with increased mortality [8-10] and may be an independent predictor of future cardiovascular events.[8-15]

The purpose of this study was to assess whether the ankle-arm index (AAI) predicts (cardiovascular) morbidity and mortality in the elderly population at large. Such information could guide the development of screening and intervention programs.

Methods

This study is part of the Rotterdam Study, a prospective cohort study designed to investigate determinants of the occurence and progression of chronic diseases in the elderly. Emphasis is on four areas of research: cardiovascular diseases, neurogeriatric diseases, locomotor diseases, and ophthalmologic diseases. The rationale and design of the study have been described previously.[16]

All individuals aged 55 years and over, living in a suburb of Rotterdam, the Netherlands (a total of 10,275 subjects), were invited to participate in the Rotterdam Study. Baseline measurements were compiled after an extensive interview at the participant's home and two visits to the research center. The overall response rate was 78% (7,983 subjects; 3,105 men and 4,878 women). Of these, 879 subjects lived in nursing homes. Baseline data, collected between 1990 and 1993, included information on history of cardiovascular disease, cardiovascular risk factors, an ankle-arm systolic blood pressure index (AAI), and an ECG. Intermittent claudication was diagnosed according to the criteria of the WHO/ Rose-questionnaire,[17] which was included in the home interview. Blood pressure was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer at the right brachial artery in sitting position. The systolic blood pressure level of the posterior tibial artery at both the

left and right leg was measured using a 8 MHz continuous wave Doppler probe (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, UK) and a random-zero sphygmomanometer.[18-23] For each leg a single blood pressure reading was taken with the subject in supine position.[24] The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm (ankle-arm index) was calculated for each leg. The lowest ankle-arm index (AAI) in either leg was used in the analysis.[2] In agreement with the approach followed by Fowkes et al [2] and by Schroll and Munck,[25] peripheral arterial disease (PAD) was considered present when the AAI was lower than 0.90 on at least one side, a threshold value that prevails in most studies.[1,2,25-27] The AAI was available in 6,450 (2,589 men and 3,861 women) participants.

Hypertension was defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.[28] Diabetes mellitus was defined as the current use of antidiabetic drugs or a random or post-load serum glucose level greater than 11.0 mmol/l, after an oral glucose tolerance test.[29] Subjects were categorized in groups of current smokers, former smokers and those who never smoked. Serum total cholesterol was determined by an automated enzymatic procedure.[30] Serum high density lipoprotein (HDL) cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium,[31] with a minor modification as described by Grove.[32] Height and weight were measured and the body mass index (kg/m^2) was calculated.

A history of myocardial infarction and stroke was obtained through direct questioning and considered positive when confirmed by a physician. A history of angina pectoris was assessed using the WHO/ Rose-questionnaire.[17] A 12-lead ECG was recorded with an ESAOTE-ACTA cardiograph with a sampling frequency of 500 Hz and stored digitally. Electrocardiographic left ventricular hypertrophy (LVH) was determined using an automated diagnostic classification system, the Modular Electrocardiogram Analysis System (MEANS), and was based on voltage, shape, and repolarisation criteria.[33,34]

The follow-up period started at the baseline examination and in the present analysis lasted until January 1996. Information considering the vital status of the participants was obtained from the municipal health service in Rotterdam. Clinical follow-up data on fatal and non-fatal endpoints were obtained from the general practitioners (GPs) working in the research area of the Rotterdam Study through linkage of the GP's automated medical record system to the data base of the Rotterdam Study on a regular basis. All possible events, including deaths, reported by the GP were regularly evaluated by research physicians reviewing medical records and discharge reports and letters of medical specialists available at the GP's office of every

participant. Cause and circumstances of death were established shortly after the reporting of death by the municipal health service or the GP. All events were classified according to the International Classification of Diseases, 10th version,[35] and coded independently by two research physicians. In case of disagreement, consensus was reached in a separate coding session. A medical expert in the field of cardiovascular disease reviewed and verified all coded events. The judgement of this expert was considered final if no consensus was reached.

Cardiac mortality was defined as death from myocardial infarction (I21-24), chronic ischaemic heart disease (I25), pulmonary embolism or other pulmonary heart disease (I26-28), cardiomyopathy (I42-43), cardiac arrest (I46), arrhythmia (I47-49), heart failure (I50), or sudden cardiac death. Sudden cardiac death was defined as death occurring instantaneously or within one hour after onset of symptoms or unwitnessed death, in which a cardiac cause could not be excluded.[36,37] Complete follow-up information was available in 92% of the 6,450 participants in which an ankle-arm index (AAI) was assessed. Participants without follow-up data, mainly because they moved to unknown addresses or no data could be collected about the vital status or date of death, were censored in the survival analyses.

Survival analyses based on the Kaplan-Meier estimate of the survival function were used to produce survival curves for all-cause and cardiovascular mortality. Cox' proportional hazards models were used to examine the risk for cardiovascular and all-cause mortality in those with an ankle-arm index (AAI)<0.90 with and without intermittent claudication, and those with an AAI ≥0.90 and intermittent claudication, taking subjects with an AAI ≥0.90 and no intermittent claudication as the reference group. The models included age and sex (Model A), or included age, sex, and other important confounders, i.e. prior myocardial infarction, stroke, smoking, or diabetes mellitus (Model B). Because the inclusion of additional potential confounders (such as blood pressure, cholesterol) did not change the risk estimated in the analyses they are not presented in the paper.

In addition, Cox' proportional hazards model was used to examine the risk for cardiovascular and all-cause mortality associated with the ankle-arm index (AAI) using different threshold values for PAD (0.50, 0.70, and 0.90), and using the AAI as a continuous variable. In the latter analysis the hazard ratios per 0.1 increase in the AAI were calculated. Finally, we examined the risk for specific fatal and non-fatal cardiovascular events associated with an AAI<0.90 (compared to an AAI ≥0.90). Analyses were performed using SPSS software (SPSS for Windows 7.5, SPSS Inc., Chicago, USA).

Table 1: General characteristics of 6,450 men and women aged 55 years and over in whom the presence of peripheral arterial disease (PAD) was assessed.

Characteristic	Men (n=2,589)	Women (n=3,861)	Total (n=6,450)
Age (years), mean (SD)*	68.3 (8.4)	70.3 (9.7)	69.5 (9.3)
Body mass index (kg/m^2), mean (SD)	25.7 (3.7)	26.7 (4.1)	26.3 (4.0)
Systolic blood pressure (mmHg), mean (SD)	139 (22)	140 (23)	139 (22)
Diastolic blood pressure (mmHg), mean (SD)	75 (12)	73 (12)	74 (12)
Hypertension (%)	26.3	32.7	30.1
Intermittent claudication (%)†	2.1	1.4	1.7
Peripheral arterial disease (%)‡	16.9	20.5	19.1
Serum total cholesterol (mmol/l), mean (SD)	6.3 (1.2)	6.8 (1.2)	6.6 (1.2)
Serum HDL cholesterol (mmol/l)§, mean (SD)	1.2 (0.3)	1.4 (0.4)	1.3 (0.4)
Smoking (%) Current	24.2	17.3	20.1
Former	59.3	27.8	40.5
Diabetes mellitus (%)	7.6	8.5	8.1
LVH¶ by Electrocardiogram (%)	10.4	6.1	7.7
History of angina pectoris (%)	6.5	6.9	6.7
History of myocardial infarction (%)	19.3	9.5	13.5
History of stroke (%)	4.7	3.9	4.2

* SD: standard deviation.
† according to the criteria of the WHO/ Rose-questionnaire.
‡ assessed by measuring the ankle-arm systolic blood pressure index (AAI), with peripheral arterial disease (PAD) present with an AAI<0.90.
§ HDL cholesterol: high density lipoprotein cholesterol.
¶ LVH: left ventricular hypertrophy.

Results

General characteristics of the participants in whom the ankle-arm index (AAI) was assessed, are given in Table 1. Of the 6,450 participants 19.1% (95% CI 18.1-20.0) had an AAI<0.90, and 1.6% (95% CI 1.3-1.9) reported symptoms of intermittent claudication.[38]

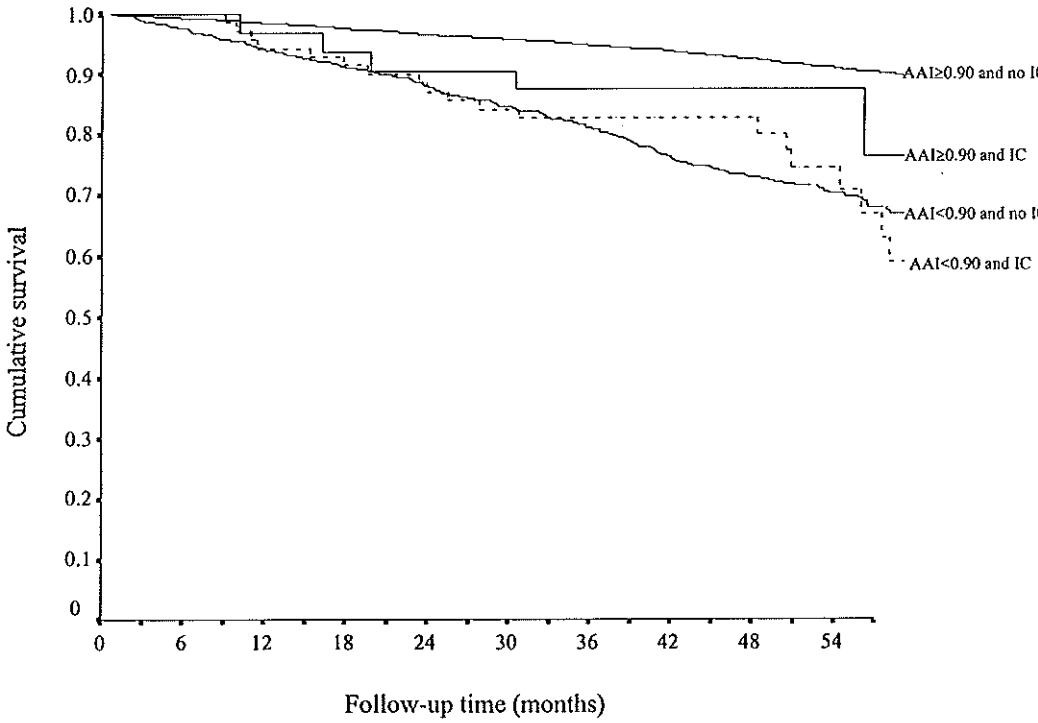

Figure 1. Kaplan-Meier survival curves for all-cause mortality in individuals with an ankle-arm index (AAI) <0.90 with or without intermittent claudication (IC), in individuals with an AAI ≥0.90 and IC, and in those with an AAI ≥0.90 and without IC.

During the mean follow-up period of 3.7 years (range 0.1-6.2 years), 725 (12.2%) participants died; 155 (2.7%) died from a cardiac cause, of which 64 developed sudden cardiac death. A myocardial infarction occurred in 217 (3.8%) subjects, of whom 51 died, and a stroke occurred in 135 (2.3%), of which 38 were fatal. Of the 725 deaths, 209 (28.8%) were due to cardiovascular causes.

In comparison to those with an ankle-arm index (AAI) ≥0.90 and no intermittent claudication, participants with both an AAI<0.90 and intermittent claudication had an age- and sex-adjusted twofold risk for all-cause mortality (hazard ratio (HR) 2.3; 95% confidence interval (CI) 1.5-3.6), those with an AAI<0.90 and no intermittent claudication had a relative risk of 1.8 (HR 1.8; 95% CI: 1.5-2.1), while in participants with an AAI ≥0.90 and complaints of intermittent claudication the HR was 1.4 (95% CI: 0.6-3.3) (Table 2). Additional adjustment for the presence of a history of myocardial infarction or stroke, smoking, and diabetes mellitus at baseline only slightly reduced the

risks. The same pattern was observed for the risk of cardiovascular mortality, both after adjustment for age and sex (model A), and after additional adjustment for potential confounders (model B) (Table 2). Kaplan-Meier survival curves for all-cause mortality in individuals with an AAI<0.90 or AAI ≥0.90 with intermittent claudication, and in individuals with an AAI <0.90 and no intermittent claudication, compared to the reference group of individuals with an AAI ≥0.90 and no intermittent claudication, are presented in Figure 1. Figure 2 shows the Kaplan-Meier survival curves for cardiovascular mortality in the same groups.

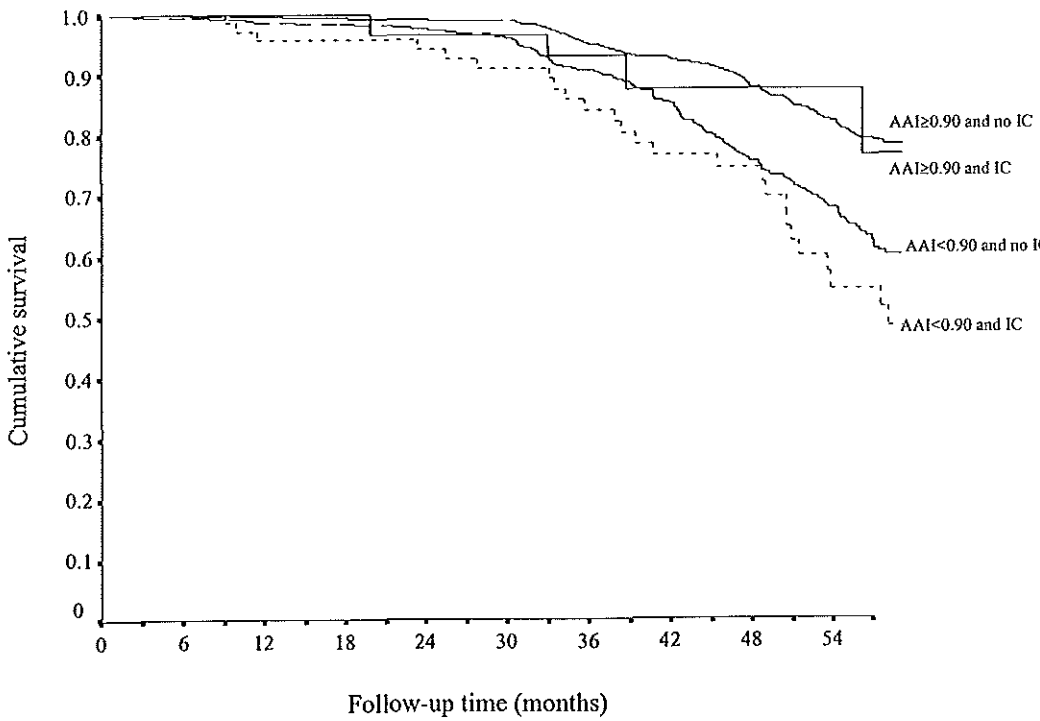

Figure 2. Kaplan-Meier survival curves for cardiovascular mortality in individuals with an ankle-arm index (AAI) <0.90 with or without intermittent claudication (IC), in individuals with an AAI ≥0.90 and IC, and in those with an AAI ≥0.90 and without IC.

An increase in mortality was observed with decrement of the AAI. The HR for all-cause mortality associated with a 0.1 decrease in the AAI was 0.90 (95% CI: 0.88-0.92), and for cardiovascular mortality 0.89 (95% CI: 0.87-0.92). The corresponding HRs after adjustment for other potential confounders were 0.91 (95% CI: 0.88-0.93),

and 0.93 (95% CI: 0.90-0.95). The same was observed when for decrease of the AAI lower threshold values were used, namely, from 1.4 (95% CI: 1.2-1.8) for an AAI between 0.90 and 0.70 to 2.6 (95% CI: 2.0-3.3) for an AAI below 0.50. Similar estimates were found for cardiovascular mortality (Table 3).

Table 2: Hazard ratios (95% confidence interval) of all-cause and cardiovascular mortality in individuals with an ankle-arm index (AAI) <0.90 with and without intermittent claudication (IC) and individuals with an AAI ≥0.90 with IC, in comparison to individuals with an AAI ≥0.90 without IC, adjusted for age and sex (Model A), and for multiple possible confounders (Model B).

	Baseline category of peripheral arterial disease (PAD)					
	AAI†<0.90 and IC*		AAI <0.90 and no IC		AAI ≥0.90 and IC	
	Model A‡	Model B§	Model A	Model B	Model A	Model B
All-cause mortality						
Men	2.7 (1.5-4.9)	2.7 (1.5-5.0)	1.6 (1.2-2.1)	1.6 (1.2-2.0)	1.5 (0.6-4.2)	1.5 (0.6-4.1)
Women	2.0 (1.1-3.8)	2.0 (1.0-3.8)	1.9 (1.5-2.4)	1.7 (1.4-2.2)	0.9 (0.1-6.6)	---¶
Total	2.3 (1.5-3.6)	2.3 (1.4-3.5)	1.8 (1.5-2.1)	1.7 (1.4-2.0)	1.4 (0.6-3.3)	1.2 (0.4-3.2)
Cardio-vascular mortality						
Men	2.5 (0.8-8.0)	2.5 (0.7-8.1)	1.2 (0.7-2.0)	1.2 (0.7-2.1)	---¶	---¶
Women	2.9 (1.5-5.3)	2.9 (0.9-9.6)	2.1 (1.3-3.4)	2.1 (1.2-3.4)	---¶	---¶
Total	2.8 (1.2-6.3)	2.6 (1.1-6.1)	1.6 (1.1-2.3)	1.6 (1.1-2.4)	---¶	---¶

* IC: intermittent claudication according to the criteria of the WHO/Rose-questionnaire.
† AAI: ankle-arm systolic blood pressure index.
‡ Model A: adjusted for age and sex.
§ Model B: adjusted for age, sex, diabetes mellitus, history of stroke, history of myocardial infarction, and smoking.
¶ Number of subjects too small for this subgroup-analysis.

In addition, we observed an increased risk for non-fatal myocardial infarction (HR 1.9; 95% CI: 1.3-2.9) and non-fatal stroke (HR 2.5; 95% CI: 1.7-3.6) in participants with an AAI<0.90, independent of age, sex or other possible confounders (Table 4).

Table 3: Hazard ratios (95% confidence interval) of all-cause and cardiovascular mortality in individuals with peripheral arterial disease defined as an ankle-arm index (AAI) <0.50, as 0.5≤ AAI <0.70, and as 0.7≤ AAI <0.90, in comparison to individuals with an AAI ≥0.90, adjusted for age and sex (Model A), and for multiple possible confounders (Model B).

	Baseline category of peripheral arterial disease (PAD)					
	AAI† <0.50		**0.5≤ AAI <0.70**		**0.7≤ AAI <0.90**	
	Model A‡	Model B§	Model A	Model B	Model A	Model B
All-cause mortality						
Men	1.9 (1.1-3.0)	1.7 (1.0-2.9)	2.1 (1.5-2.9)	2.0 (1.4-2.9)	1.4 (1.0-1.9)	1.3 (0.9-1.8)
Women	3.0 (2.2-4.1)	2.8 (2.0-4.1)	2.0 (1.5-2.7)	1.9 (1.4-2.6)	1.5 (1.1-1.9)	1.4 (1.1-1.9)
Total	2.6 (2.0-3.3)	2.3 (1.7-3.1)	2.0 (1.6-2.5)	1.9 (1.5-2.4)	1.4 (1.2-1.8)	1.4 (1.1-1.7)
Cardio-vascular mortality						
Men	---¶	---¶	1.1 (0.5-2.5)	1.1 (0.5-2.8)	1.2 (0.7-2.3)	1.3 (0.7-2.5)
Women	3.4 (1.6-6.9)	---¶	2.6 (1.4-4.9)	2.3 (1.2-4.5)	1.6 (0.8-2.9)	1.6 (0.8-3.0)
Total	2.1 (1.2-3.8)	---¶	1.8 (1.1-2.9)	1.6 (1.0-2.8)	1.3 (1.3-1.9)	1.4 (0.9-2.2)

† AAI: ankle-arm systolic blood pressure index.
‡ Model A: adjusted for age and sex.
§ Model B: adjusted for age, sex, diabetes mellitus, history of stroke, history of myocardial infarction, and smoking.
¶ Number of subjects too small for this subgroup-analysis.

Table 4: Hazard ratios (95% confidence interval) of non-fatal and fatal cardiovascular events in individuals with peripheral arterial disease (PAD) defined as an ankle-arm index (AAI) <0.90 compared to individuals with an AAI ≥0.90, adjusted for age and sex, and additionally for a history of myocardial infarction or stroke, smoking, and diabetes mellitus at baseline.

	Adjusted for age and sex	Adjusted for age, sex, myocardial infarction, and stroke	Adjusted for age, sex, myocardial infarction, stroke, smoking, and diabetes mellitus
Non-fatal events			
Myocardial infarction	1.9 (1.3-2.9)	1.8 (1.2-2.8)	1.8 (1.2-2.7)
Stroke	2.5 (1.7-3.6)	2.4 (1.7-3.5)	2.3 (1.5-3.3)
Fatal events			
Myocardial infarction	2.2 (1.2-4.0)	1.9 (1.0-3.5)	1.5 (0.8-2.9)
Stroke	2.0 (1.0-3.9)	1.7 (0.8-3.4)	1.5 (0.7-3.1)
All cardiovascular deaths	1.8 (1.6-2.1)	1.4 (1.2-1.6)	1.4 (1.2-1.7)

Discussion

The findings in our study suggest that the ankle-arm systolic blood pressure index (AAI) is a strong and independent predictor of subsequent all-cause and cardiovascular mortality and non-fatal cardiovascular events in the elderly. The risk of mortality is about two times higher in those with an AAI<0.90, even in those without complaints of intermittent claudication. With the AAI marked as an indicator of generalised atherosclerosis, one would expect a graded relationship to cardiovascular mortality and morbidity with a decreasing AAI. In our study we found such a relationship when different threshold values for the AAI to define PAD were used, and when including the AAI as a continuous variable in the multivariate analyses.

As in most studies, we used a single measurement of the AAI to define PAD. This may have underestimated the actual risk, because taking the mean of consecutive measurements would reduce the difference between the measured AAI and the actual AAI (due to regression towards the mean) yielding a higher relative risk per unit of change in the AAI.

The increased risk for mortality with an AAI<0.90 has also been reported by other authors.[4,8-15] We found an increasing risk of mortality with lower thresholds for the AAI strongly suggesting that a lower AAI reflects more advanced generalized atherosclerosis. An AAI threshold of 0.90 is, however, preferable for screening purposes because it identifies asymptomatic individuals with early signs of PAD. Subjects with an AAI<0.90 were also at a higher risk of developing subsequent non-fatal cardiovascular events compared to those with an AAI ≥0.90. All findings were independent of age, sex, and the presence of relevant cardiovascular confounders. As in the study by Leng et al,[13] non-fatal stroke in subjects with an AAI<0.90 was more common than non-fatal myocardial infarction (MI).

In conclusion, the ankle-arm index (AAI) is a strong, independent predictor of cardiovascular and all-cause mortality and non-fatal MI and stroke in the elderly. This simple non-invasive technique could be included as a screening device in cardiovascular risk management, and thus play a role in the prevention of cardiovascular morbidity and mortality.

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Chapter 8

Targeting of Screening for Peripheral Arterial Disease in Primary Care

Manuscript based on chapter 8:

Meijer WT, Grobbee DE, Hofman A, Hoes AW. Targeting of screening for peripheral arterial disease in general practice. The Rotterdam Study. J Clin Epidemiol (accepted).

Introduction

Peripheral arterial disease (PAD) is a relatively common disorder in the elderly. In a minority of cases this chronic disorder becomes symptomatic as intermittent claudication: pain in the calf of the leg, induced by walking, and relieved by standing still.[1-3]

Detection of PAD is useful because on the one hand life expectancy in patients with PAD is reduced, and the incidence of cardiovascular disease is clearly increased,[4-8] also in subjects without intermittent claudication,[4,9,10] and on the other hand interventions aimed at improving the cardiovascular risk profile of these patients or prescription of antiplatelet drugs could favourably influence prognosis.

PAD is relatively easy to assess by means of the ankle-arm systolic blood pressure index (AAI), a commonly used and valid non-invasive test.[11,12] The AAI can be measured using a Doppler device. Many Dutch general practitioners have a Doppler device (around 40% [13]), but the device is not often used for this purpose.

It remains unclear, whether screening for PAD should be targeted at every individual, or whether screening of a subgroup of individuals is preferable.

We determined whether expensive, time-consuming population screening or preselection based on patient characteristics commonly available in medical practice (such as age, gender, and medical history) produces the highest screening yield, among men and women aged 55 years and over.

Methods

This study is part of the Rotterdam Study, a prospective follow-up study designed to investigate determinants of the occurrence and progression of chronic diseases in the elderly. Emphasis is on four areas of research: cardiovascular diseases, neurogeriatric diseases, locomotor diseases and ophthalmologic diseases. The rationale and design of the study have been described previously.[14]

All individuals aged 55 years and over, living in the suburb of Ommoord in Rotterdam (n= 10,275), were invited to participate. Baseline measurements comprised an extensive interview at the participant's home and two visits to the research center. The overall response rate was 78 percent (7,983 subjects; 3,105 men and 4,878 women). Of these, 879 subjects lived in nursing homes.

Intermittent claudication was diagnosed according to the criteria of the WHO/ Rose-questionnaire,[15] which was included in the home interview. The prevalence of

intermittent claudication was assessed in 7,715 participants in whom the answers to the Rose questionnaire were available. Intermittent claudication was reported by 1.6 percent (95% CI: 1.3-1.9) of all participants.[16]

Blood pressure was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer at the right brachial artery in sitting position. The systolic blood pressure level of the posterior tibial artery was measured at both the left and right leg using an 8 MHz continuous wave Doppler probe (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, UK) and a random-zero sphygmomanometer.[17-21] For each leg a single blood pressure reading was taken with the subject in supine position. The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm (ankle-arm index) was calculated for each leg as a measure of peripheral arterial disease. The lowest ankle-arm index (AAI) in either leg was used in the analysis.[9] In agreement with the approach followed by Fowkes et al [9] and by Schroll and Munck,[22] peripheral arterial disease was considered present when the AAI was lower than 0.90 at at least one side. The AAI was not determined in 1,533 participants; 824 subjects did not visit the research center, 4 subjects had died before their visit to the center, and in 705 subjects the systolic arm blood pressure (n=7), or the systolic ankle blood pressure (n=559) or both (n=139) were not measured. The characteristics of these 705 individuals did not differ appreciably from the population in which the AAI could be determined. Thus, the AAI was calculated in 6,450 participants (2,589 men and 3,861 women).

During the baseline examinations, established cardiovascular risk indicators and the presence (or absence) of symptomatic cardiovascular disease were recorded for all participants.[14] Hypertension was defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or current use of antihypertensive drugs for the indication hypertension.[23] Diabetes mellitus was defined as the current use of antidiabetic drugs or a random or post-load serum glucose level greater than 11.0 mmol/l.[24,25] Subjects were categorized as current smokers, former smokers or those who had never smoked. Serum total cholesterol was determined by an automated enzymatic procedure in a non-fasting blood sample.[26] Serum high density lipoprotein (HDL) cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium. Height and weight were measured and the body mass index (kg/m^2) was calculated. A history of myocardial infarction and stroke was obtained through direct questioning and considered positive when confirmed by a treating physician. A history of angina pectoris was assessed using the WHO/ Rose-questionnaire.[15] Electrocardiographic left ventricular hypertrophy (LVH) was determined using an automated diagnostic classification system of the Modular

Electrocardiogram Analysis System (MEANS) in which LVH diagnosis is based on voltage, shape and repolarisation criteria.[27,28] Heart failure was defined as current use of medication for the indication heart failure.

To establish whether the number of subjects selected for screening for peripheral arterial disease (PAD) can be reduced, while still detecting most subjects with PAD, three risk functions were developed. The first risk function was based on age and gender. These variables are routinely available for practicing physicians and are important determinants for PAD; in most studies men have a higher probability of having PAD, and the prevalence of PAD clearly increases with age.[9,22,29-31] In the second risk function findings from a structured medical questionnaire were included, besides age and gender. The following items were considered: intermittent claudication (yes/no), angina pectoris (yes/no), a history of myocardial infarction (yes/no), heart failure (yes/no), a history of stroke (yes/no) and smoking behaviour (current/former vs. never). The third risk function incorporated all cardiovascular information commonly obtainable in a general practice setting; i.e. variables included in the previous two risk functions and variables requiring additional measurements, such as systolic and diastolic blood pressure (mmHg), body mass index (kg/m^2), serum glucose level (mmol/l), serum total cholesterol level (mmol/l) and electrocardiographic left ventricular hypertrophy (LVH).

Univariate odds ratios (with their 95% confidence intervals), positive predictive values, sensitivity and specificity were calculated for all risk indicators considered for inclusion in the risk functions. Age- and gender-adjusted odds ratios with standard errors were calculated using a logistic regression model with the presence of peripheral arterial disease as the dependent variable. Risk indicators with an age- and gender-adjusted coefficient/standard error ratio of 1.5 or more or -1.5 or less were entered in a multivariate logistic regression model together with the other variables selected for that risk function.

The general formula of a risk function based on logistic regression analyses is: $p(PAD) = 1/[1+\exp(-(b_0+b_{1...n}X_{1...n}))]$ where p(PAD) is the probability of a subject of having peripheral arterial disease (PAD), b_0 is the intercept in the logistic equation, $b_{1...n}$ denote the logistic coefficients of the variables X_1 to X_n, and $X_{1...n}$ represent the value of the variable $X_{1...n}$ in a particular subject. In case of a dichotomous variable this value is 1 in the presence, and 0 in the absence of the risk indicator. In order to visualize the performance of each risk function to predict the presence of peripheral arterial disease (PAD), receiver operator characteristic (ROC) curves were plotted, and areas under the ROC-curves (AUC) were estimated.[32-34] To determine the effectiveness of either risk function in preselecting persons with an increased risk of PAD for measurement of the

AAI, the overall sensitivity (i.e. proportion of subjects with PAD that is selected for measurement of the AAI and thus detected), specificity (i.e. proportion of subjects without PAD that is not selected for measurement of the AAI), and the proportion of the total population selected for measurement of the AAI were estimated. These parameters were calculated for all three risk functions using a 15%, 20%, and 25% estimated probability of an individual to have PAD as cut-off points above which measurement of the AAI is indicated. All analyses were performed using BMDP software (BMDP Statistical Software, Inc., Los Angeles).

Table 1: General characteristics of 6,450 men and women aged 55 years or over in whom the presence of peripheral arterial disease was assessed.

Characteristic		Men (n=2,589)		Women (n=3,861)	
Age (years), mean (SD)*		68.3	(8.4)	70.3	(9.7)
Body mass index (kg/m^2), mean (SD)		25.7	(3.7)	26.7	(4.1)
Systolic blood pressure (mmHg), mean (SD)		139	(22.0)	140	(23.0)
Diastolic blood pressure (mmHg), mean (SD)		75	(12.0)	73	(12.0)
Peripheral arterial disease (%)†		16.9		20.5	
Intermittent claudication (%)‡		2.1		1.4	
Hypertension (%)		26.3		32.7	
Diabetes mellitus (%)		7.6		8.5	
Smoking (%)	Current	24.2		17.3	
	Former	59.3		27.8	
Serum total cholesterol (mmol/l), mean (SD)		6.3	(1.2)	6.8	(1.2)
Serum HDL cholesterol (mmol/l),§ mean (SD)		1.2	(0.3)	1.4	(0.4)
History of angina pectoris (%)		6.5		6.9	
History of myocardial infarction (%)		19.3		9.5	
History of stroke (%)		4.7		3.9	
Heart failure (%)		4.2		6.1	

* SD: standard deviation.
† defined as an ankle-arm systolic blood pressure index (AAI) <0.90.
‡ according to the criteria of the WHO/ Rose-questionnaire.
§ HDL cholesterol: high density lipoprotein cholesterol.

Results

In Table 1, selected characteristics of the study population are given for men and women separately. Peripheral arterial disease (PAD), defined as an AAI < 0.90, was present in 19.1% (95% CI 18.1-20.0) of all participants. The mean ankle-arm systolic blood pressure index (AAI) was 1.05 (standard deviation (SD) 0.23); the age-adjusted estimates for men and women were 1.08 (SD 0.24) and 1.03 (SD 0.23), respectively.[16]

In both men and women, age 75 years and over (OR 4.6), diabetes mellitus (OR 2.5), hypertension (OR 2.1), intermittent claudication (OR 11.2, OR for women 10.2), heart failure (OR 2.7, OR for women 2.2), and a positive history of stroke (OR 3.0, OR for women 4.1) yielded univariate odds ratios greater or equal to 2, supporting that these variables may be used as risk indicators for peripheral arterial disease (Tables 2 and 3). The multivariate analysis produced similar results (Table 4).

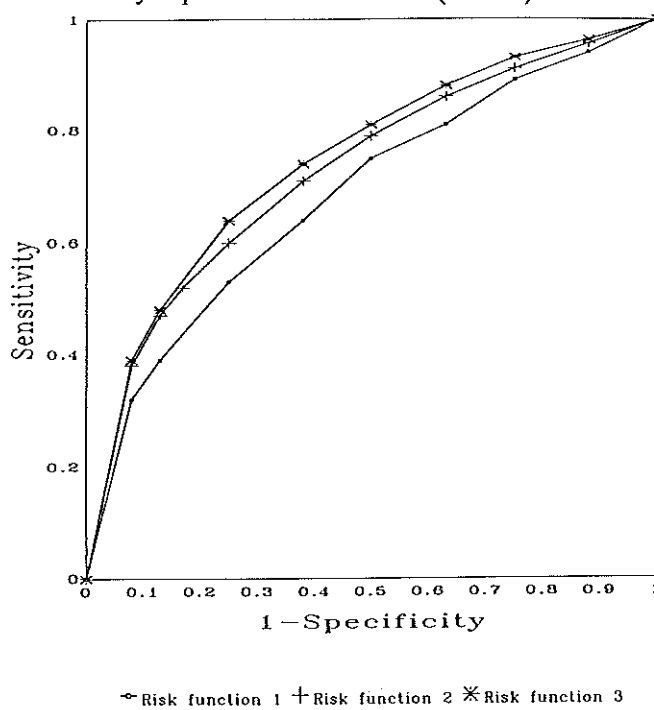

Figure 1: Receiver operating characteristic (ROC) curves of the three risk functions predicting the presence of peripheral arterial disease (PAD). Risk function 1 includes age and gender, risk function 2 includes age, gender, and data from a structured medical questionnaire, and risk function 3 also includes systolic and diastolic blood pressure, body mass index, serum glucose level, serum total cholesterol level and findings from a 12-lead ECG.

In Figure 1 the receiver operating characteristic (ROC) curves for the three risk functions are given. The area under the curve (AUC) was 0.69 for the first risk function (age and gender), while the AUC for the second and the third risk functions were 0.74 and 0.76, respectively.

Table 2: Odds ratio (OR) and 95% confidence interval (95% CI), positive predictive value, sensitivity and specificity of cardiovascular risk indicators in 2,589 men aged 55 years or over in whom the presence of peripheral arterial disease (PAD) was assessed.

Risk factor		OR	95% CI	PPV*	Sensitivity	Specificity
Age (years)	≤ 70	0.31	0.25-0.39	14.1 %	39.2 %	33.2 %
	> 70	3.18	2.57-3.93	44.8 %	61.3 %	66.8 %
BMI† ≥ 30.0 kg/m^2		0.85	0.55-1.29	14.4 %	6.2 %	92.8 %
Serum total cholesterol ≥ 6.5 mmol/l		0.86	0.70-1.07	15.6 %	38.7 %	57.7 %
Smoking	Current	2.33	1.85-2.88	26.6 %	38.8 %	78.7 %
	Former	0.50	0.41-0.63	12.7 %	45.2 %	37.9 %
Diabetes mellitus		1.88	1.22-2.59	24.7 %	12.2 %	93.8 %
Hypertension		2.01	1.57-2.60	24.6 %	38.6 %	76.2 %
History of intermittent claudication		11.24	6.30-19.8	67.3 %	8.7 %	99.2 %
History of myocardial infarction		1.86	1.43-2.58	24.7 %	21.1 %	87.5 %
History of angina pectoris		1.59	1.09-2.30	23.4 %	9.2 %	94.0 %
LVH‡ by ECG§		1.26	1.11-1.34	24.8 %	13.5 %	90.4 %
Heart failure		2.70	1.80-4.51	34.1 %	8.6 %	96.6 %
History of stroke		3.01	2.02-4.43	35.6 %	10.1 %	96.4 %

* PPV: positive predictive value; i.e. the proportion of patients selected for screening with the ankle-arm index (AAI) that actually has an AAI lower than 0.90.
† BMI: body mass index.
‡ LVH: left ventricular hypertrophy.
§ ECG: electrocardiogram.

If a probability of having peripheral arterial disease (PAD) of 15% is chosen as the cut-off point above which screening, and thus measurement of the AAI, is indicated,

a sensitivity in the range of 44% to 78% is achieved. This means that 44-78% of all subjects with PAD (AAI < 0.90) will be detected, depending which risk function is used. To achieve such sensitivity 19% to 57% of the subjects need to be selected for AAI measurements (Table 5).

Table 3: Odds ratio (OR) and 95% confidence interval (95% CI), positive predictive value, sensitivity and specificity of cardiovascular risk indicators in 3,861 women aged 55 years or over in whom the presence of peripheral arterial disease (PAD) was assessed.

Risk factor		OR	95% CI	PPV*	Sensitivity	Specificity
Age (years)	≤ 70	0.26	0.22-0.31	11.7 %	27.6 %	40.6 %
	> 70	3.84	3.23-4.55	57.1 %	72.4 %	59.4 %
BMI† ≥ 30.0 kg/m^2		0.94	0.77-1.17	18.7 %	18.7 %	80.3 %
Serum total cholesterol ≥6.5 mmol/l		0.92	0.79-1.09	19.6 %	59.1 %	38.9 %
Smoking	Current	1.21	0.97-1.47	22.5 %	19.6 %	83.2 %
	Former	0.82	0.68-0.98	17.7 %	24.7 %	71.4 %
Diabetes mellitus		2.30	1.78-2.99	36.0 %	12.3 %	94.7 %
Hypertension		2.12	1.80-2.63	28.9 %	46.6 %	70.9 %
History of intermittent claudication		10.23	5.58-18.6	70.6 %	4.9 %	99.5 %
History of myocardial infarction		2.43	1.74-3.35	35.6 %	9.9 %	95.7 %
History of angina pectoris		1.41	1.04-1.88	25.2 %	8.8 %	93.6 %
LVH‡ by ECG§		2.06	1.98-2.14	37.5 %	9.8 %	95.0 %
Heart failure		2.23	1.56-3.12	33.8 %	10.6 %	94.9 %
History of stroke		4.13	2.96-5.76	48.3 %	9.7 %	97.5 %

* PPV: positive predictive value; i.e. the proportion of patients selected for screening with the ankle-arm index (AAI) that actually has an AAI lower than 0.90.
† BMI: body mass index.
‡ LVH: left ventricular hypertrophy.
§ ECG: electrocardiogram.

With a lower cut-off point (e.g. 5%) the sensitivity of the risk functions, especially risk function 1, increases to 100%, but then almost all subjects would be selected for AAI measurements.

If a cut-off point of 15% is used, the results of risk function 1 seem preferable over the results of the other risk functions, with 57% of the subjects selected for screening, and a reasonable balance between sensitivity (subjects with PAD actually detected, 78%) and specificity (subjects without PAD not screened with the AAI, 47%). Also with the choice of 20% as the cut-off a point, risk function 1 seems preferable. This risk function, based on age and gender only, is far easier to use, and less expensive than the other risk functions.

Table 4: Cardiovascular risk indicators of peripheral arterial disease (PAD) with odds ratios (OR) and 95% confidence intervals (95% CI) included in three different risk functions. Results of multiple logistic regression.

	Risk function 1	Risk function 2	Risk function 3
Variable	OR (95% CI)	OR (95% CI)	OR (95% CI)
Gender	1.14 (1.00-1.31)	1.34 (1.14-1.58)	1.21 (1.01-1.45)
Age >70 years	3.57 (3.12-4.07)	2.99 (2.55-3.52)	2.65 (2.23-3.16)
History of intermittent claudication		10.46 (6.27-17.46)	10.14 (5.91-17.39)
History of myocardial infarction		1.80 (1.45-2.25)	1.79 (1.42-2.25)
Heart failure		1.60 (1.20-2.14)	1.49 (1.08-2.04)
History of stroke		2.76 (2.01-3.81)	2.41 (1.70-3.40)
Smoking (current vs. never)		2.11 (1.76-2.53)	2.11 (1.74-2.55)
Hypertension			1.82 (1.54-2.16)
Diabetes mellitus			1.64 (1.25-2.14)
Serum total cholesterol ≥6.5 mmol/l			1.18 (1.00-1.40)
LVH* by ECG†			1.17 (1.09-1.25)

* LVH: left ventricular hypertrophy.
† ECG: electrocardiogram.

Table 5. Proportion of subjects selected for measurement of the ankle-arm systolic blood pressure index (AAI), sensitivity and specificity of the three risk functions* to predict the presence of peripheral arterial disease (PAD).

	Risk function 1	Risk function 2	Risk function 3
p(PAD)† ≥ 15%			
Selected for screening	57%	38%	19%
Sensitivity‡	78%	64%	44%
Specificity§	47%	65%	83%
p(PAD) ≥ 20%			
Selected for screening	39%	24%	14%
Sensitivity	65%	52%	34%
Specificity	66%	81%	88%
p(PAD) ≥ 25%			
Selected for screening	26%	16%	10%
Sensitivity	54%	41%	28%
Specificity	79%	87%	92%

* The general formula of a risk function is: $p(PAD) = 1/[1+\exp(-(b_0+b_{1...n}X_{1...n}))]$ where p(PAD) is the probability of a subject of having peripheral arterial disease (PAD), b_0 is the intercept in the logistic equation, $b_{1...n}$ denote the logistic coefficients of the variables X_1 to X_n, and $X_{1...n}$ represent the value of the variable $X_{1...n}$ in a particular subject.

† p(PAD): probability that peripheral arterial disease (PAD) is present, estimated by either risk function. Calculations were made by assuming different cut-off points (15%, 20% and 25%) for an individual's risk of PAD above which measurement of the ankle-arm index (AAI) is indicated.

‡ Sensitivity: proportion of subjects with PAD that is selected for screening, and also detected.

§ Specificity: proportion of subjects without PAD that is not selected for measurement of the AAI.

Besides using risk functions one could use specific selection criteria, such as age over 70 years, having diabetes mellitus, or current smoking. The highest detection rate of PAD cases (47%) is achieved when all women over 70 years of age from our study population are selected for screening, corresponding to 28% of all subjects aged 55 years and over.

Discussion

Our study suggests that with the use of a risk function based on age and gender, the majority of subjects with peripheral arterial disease (PAD) can be detected (78%), while about half of the population would require screening with the ankle arm systolic blood pressure index (AAI).

The AAI is a relatively easy, and non-invasive measure to assess presence of PAD, and largely identifies asymptomatic individuals. Based on the conclusions of Hiatt et al,[35] we used the ankle-arm index at rest as an indicator of PAD, with PAD defined present when the AAI was lower than 0.90, a threshold value that prevails in most studies. A threshold value of 0.90 is up to 95% sensitive and about 100% specific in detecting angiogram-positive disease,[36] and is related to the severity of the disease.[37] A close relationship between the AAI and the results of duplex scanning of the major arteries of the leg has been documented.[38] Recently, the AAI was promoted by Fowkes et al to be used as marker of asymptomatic atherosclerosis.[39]

In analogy with other studies, we used a single measurement of the AAI to define PAD. The repeatability of the AAI is such that a single measurement seems suitable for most epidemiologic studies.[40] In addition, Stoffers et al showed that the AAI is a valid measure of PAD, suitable for diagnostic purposes in general practice.[12,41]

One could argue whether detection of 78% of all PAD cases is enough, because 57% of the population would require screening to achieve such a detection rate. In practice this would mean that every GP should screen about two thirds of his patients aged 55 years and over to detect most of his PAD cases. To apply such a risk function one has to develop a simple algorithm for computer use or create a table to allow for preselection.

Is it not easier for a GP to invite a specific subgroup of patients, based on gender, age or morbidity? In our study only invitation of all women over 70 years of age (28% of the study population would be screened, giving a detection rate of 47%) could be potentially useful. Screening of all other subgroups, e.g. men over 70 years of age, men or women with diabetes, etc, yields lower detection rates.

We conclude that the application of a risk function based on age and gender can reduce the number of subjects invited for screening with the ankle arm systolic blood pressure index (AAI), while still detecting most PAD cases. In the Rotterdam Study no vascular physical examination was performed. Although, in theory addition of physical signs (such as bruits, peripheral pulsations, etc) could increase the performance of the risk functions and could therefore increase the effectiveness of screening, the validity of diagnosing PAD, based on physical examination, is limited. Stoffers et al showed that

only in symptomatic PAD patients determination of peripheral pulsations is relevant.[42] In addition, the inter-observer variability in the determination of absent peripheral pulsations is considerable.[35,43]

The AAI is a major independent risk indicator for cardiovascular morbidity and mortality and easily measurable. Identification of patients with (usually asymptomatic) PAD is important in view of the potential benefit of improving the cardiovascular risk profile in those patients and possibly the introduction of antiplatelet therapy.[44,45] The use of the AAI in medical practice, however, is limited. Perhaps the preselection based on algorithms such as presented here could promote appreciation by practising physicians of this non-invasive measure of atherosclerosis.

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Chapter 9

General Discussion

Introduction

Peripheral arterial disease (PAD) is an important manifestation of atherosclerosis, which is one of the major health problems in the world.[1] Although in the Netherlands, as in all western countries, cardiovascular mortality due to atherosclerosis shows a decline, the current burden of atherosclerosis is strongly reflected in a rise in cardiovascular morbidity.[2-4] In 1994 US$ 814 million (€ 760 million) was spent on the management of coronary heart disease (CHD) and another US$ 1,054 million (€ 984 million) on stroke in the Netherlands,[5] and in 1996 more than US$ 259 billion (€ 242 billion) on both CHD and stroke in the USA.[6]

PAD is asymptomatic in early stages. When it becomes symptomatic, it usually presents itself as intermittent claudication: ischemic pain in the calf of the leg induced by walking and relieved by standing still. PAD is considered a manifestation of generalized atherosclerosis and individuals with PAD, both symptomatic (i.e. intermittent claudication) and asymptomatic, are at an increased risk of cardiovascular mortality and major cardiovascular events.[7-9] The ankle-arm systolic blood pressure index (AAI) is a simple non-invasive tool to assess PAD. In theory, the use of this tool would facilitate early recognition, and preventive measures, of subjects with peripheral atherosclerotic disease in medical practice.[10] In current clinical practice, however, the AAI is only occasionally measured, and symptoms of intermittent claudication are used to indicate PAD. This is partly attributable to the relative lack of studies on the epidemiology of PAD. The studies presented in this PhD-thesis contribute further to the knowledge concerning the epidemiology of this manifestation of atherosclerosis.

Occurrence

Within the framework of a large population-based cohort of men and women aged 55 years or over, we were able to further quantifiy the occurrence of PAD. As in most studies, we used a single measurement of the AAI at every occasion (baseline and follow-up measurements) to define PAD. The use of a single measurement has several disadvantages. Notably, as a result of 'regression to the mean' misclassification is more prevalent than when taking the mean of consecutive measurements during each occasion. Also, the non-participants who refused to participate or could not be reached, could have reduced our estimates, assuming that the prevalence in these subjects is higher.

The prevalence of PAD (defined as an AAI <0.90 in at least one leg) we observed was 19%, while the prevalence of intermittent claudication was 2%. This illustrates the limitations of defining PAD as the presence of intermittent claudication symptoms. The prevalence observed in the Rotterdam Study would imply that as much as 686,000 individuals in the Netherlands alone, have a reduced AAI and are at an increased risk of cardiovascular events.

To this date, only few studies have reported incidence rates of PAD assessed by means of the AAI. The incidence rate of PAD in the Rotterdam Study, 23 per 1,000 person years, was high and very similar in men and women. This estimate implies that each year in about 83,000 individuals in the Netherlands alone, the AAI would decrease below 0.90.

Of interest is that women with PAD less often reported symptoms of intermittent claudication (5%) than men (9%). Possibly, women more frequently present atypical symptoms from ischaemic disease, as has been illustrated for CHD,[11] than men.

The message from our prevalence and incidence studies is that PAD affects many older adults, while the vast majority of PAD is unknown (i.e. asymptomatic) in clinical practice. Thus, the conclusion that clinicians should focus more on the detection of PAD patients seems reasonable. Detection of (asymptomatic) PAD cases, however, is only of value if it eventuates in consequences for the management of these patients. This depends on the prognostic implications of, in particular asymptomatic, PAD, and available therapeutic options.

Prognosis

The observation that the AAI is a strong and independent predictor of mortality and cardiovascular events[12-16] was confirmed by our findings. The risk of mortality is about two times higher in those with an AAI <0.90, even in those without complaints of intermittent claudication. A graded relationship between the AAI and cardiovascular mortality and morbidity was observed, suggesting that a lower AAI reflects more advanced generalized atherosclerosis. For diagnostic as well as screening purposes, dichotomization of the AAI seems preferable and a threshold of 0.90 is used more frequently. Apart from cardiovascular mortality, an AAI <0.90 also predicted future non-fatal cardiovascular events in our study, independent of age, sex, and the presence of relevant cardiovascular confounders.

Etiology

Our findings confirm the importance of cardiovascular risk factors in the etiology of PAD, because they showed a strong association with PAD and explained almost 60% of the occurrence of PAD in our study. The positive association between fibrinogen level and PAD, even after adjustment for smoking, support earlier findings of the Edinburgh Artery Study [17] that fibrinogen level has an independent role in atherogenesis in relation to PAD. A subsequent study on the role of glucose metabolism in PAD showed that insulin does not play a direct role in the progression of PAD but confirmed the importance of elevated serum glucose as a risk factor for atherosclerotic disease. A recent cross-sectional study found similar associations by using another measure of atherosclerosis, carotid intima media thickness.[18]

Approximately 40% of the etiology of PAD is not attributable to the cardiovascular risk factors included in our study. More research is needed on the role of hematological factors in the etiology of PAD, and on genetic risk factors, gene-environment interaction, and the role of inflammatory agents in atherogenesis.[19] In addition, possible protective factors for the development of PAD, such as moderate alcohol intake,[20] deserve further study.

Consequences for medical practice

The high occurrence rate of PAD in the elderly, together with an unfavourable cardiovascular risk profile and increased risk of future non-fatal and fatal cardiovascular events in PAD patients, reflects the magnitude of the problem. The question arises whether prevention, and/or early recognition of peripheral arterial disease should be stimulated and whether early therapeutic interventions should be advocated.

Prevention for PAD could be implemented in a similar fashion as guidelines on the primary prevention of other atherosclerotic diseases such as coronary heart disease (CHD): e.g. lifestyle advice (cessation of smoking, more physical exercise, etc), lowering of high blood pressure and lowering of high serum cholesterol.

Routine use of pharmacotherapy for symptomatic PAD (i.e. intermittent claudication) is still under debate. Randomized trials fail to show significant average benefit of established drugs (such as pentoxifylline, cilostazol) for patients with intermittent claudication. Studies on the effects of exercise therapy [21] demonstrate that supervised exercise programs can improve walking distance in intermittent claudication patients, but more research is needed to establish the most cost-effective exercise

programs and to identify subgroups of patients most likely to benefit. Risk factor modification (e.g. cessation of smoking, lipid modification), needs to be evaluated further because in particular cessation of smoking [22] correlates with symptomatic PAD (i.e. intermittent claudication) as well as with asymptomatic PAD. Special programs on cessation of smoking are important in the management of PAD, and the yield of such programs must be improved.

Empirical data on the effects of interventions on the prevention of development or progression, or prevention of future cardiovascular events (e.g. CHD, stroke, TIA), in asymptomatic PAD cases are very scarce. Notably the value of antiplatelet or lipid-lowering agents,[23,24] deserves further study. This would facilitate development and implementation of future management guidelines on PAD, e.g. similarly as has been the case for guidelines on hypercholesterolemia [25] and hypertension.[26] Evidence from trials on benefits of pharmacologic therapy in prevention has to be awaited before strategies, such as antiplatelet therapy in low risk subjects, can be employed in routine medical practice. Also the relative cost-effectiveness of various strategies to detect PAD, including the screening of large groups of older adults, needs to be evaluated.

At present, some researchers argue that the presence of (even asymptomatic) PAD should be considered as cardiovascular event, such as a history of MI or stroke. This implies that concomitant abnormalities in e.g. lipid metabolism (elevated LDL and triglyceride levels, low HDL level) or blood pressure, should be detected and treated more actively and at an earlier stage. In fact, such an approach is already recommended in current international and Dutch guidelines on hypercholesterolemia.[25,27]

Conclusions

Because peripheral arterial disease (PAD) is common and often asymptomatic, notably among the elderly, and leads to a poor prognosis, future research should focus on both the etiology, and possible intervention schemes to guide prevention of early stages of PAD, or possible future cardiovascular events. Screening for PAD in clinical practice could be worthwhile because early intervention could improve the cardiovascular risk profile of PAD patients. Thus, the focus in clinical practice should be not only on symptomatic, but also on asymptomatic PAD.

To detect those 'at risk' a precise measure of subclinical PAD is necessary. The ankle-arm index (AAI), considered as a marker of generalized atherosclerosis,[8] is suitable for screening purposes in medical practice. The use of the AAI as a risk indicator in cardiovascular risk profiling deserves to be stimulated in view of the challenge of preventing cardiovascular events in the elderly.

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Chapter 10

Summary

Summary

In the Netherlands, as in most western countries, cardiovascular mortality due to atherosclerosis has declined in the past two decades, but there is a clear increase in cardiovascular morbidity, in particular in the elderly. Atherosclerosis is the most common cause of peripheral arterial disease (PAD), a chronic occlusive disease of the arterial system distal to the aortic bifurcation. PAD is asymptomatic in the early stages, and when it becomes symptomatic usually presents itself as intermittent claudication. PAD is a major health problem in the elderly, because the prevalence increases sharply with age, and subjects with PAD experience a higher incidence of fatal and non-fatal events. Compared to other manifestations of atherosclerotic disease as coronary heart disease (CHD), only few population-based studies have focused on the epidemiology of PAD. In particular, studies on the incidence and prognosis (and their determinants) of PAD are scarce (Chapter 1).

The aim of the studies presented in this PhD-thesis was to further explore the clinical epidemiology of PAD in the elderly. Results presented in this dissertation are based on baseline (Rotterdam Study-1: 1990-1993) and follow-up data (Rotterdam Study-2: 1993-1995, and Rotterdam Study-3: 1997-1999) of the Rotterdam Study, a single-center, prospective, follow-up study of a large cohort of subjects, aged 55 years and over, living in the suburb of Ommoord in Rotterdam, the Netherlands. The baseline response rate was 78% (n=7,983; 3,105 men and 4,878 women). The presence of PAD and intermittent claudication was assessed by measuring the ankle-arm systolic blood pressure index (AAI) and by means of the WHO/Rose questionnaire, respectively. PAD was considered present when the AAI was lower than 0.90 in either leg. Clinical follow-up data on fatal and non-fatal endpoints were obtained from the general practitioners (GPs) working in the research area of the Rotterdam Study through linkage of the GP's automated medical record system to the data base of the Rotterdam Study on a regular basis.

The age- and sex-specific prevalence of PAD was 19.1% (95% confidence interval (CI): 18.1-20.0); 16.9% in men and 20.5% in women (Chapter 2). Symptoms of intermittent claudication were reported by 1.6% (95% CI: 1.3-1.9) of the study population (2.2% in men, 1.2% in women). Of those with PAD, 6.3% reported symptoms of intermittent claudication (8.7% in men, 4.9% in women), whereas in 68.9% of those with intermittent claudication an AAI below 0.90 was found. Subjects with an AAI lower than 0.90 were more likely to be smokers and to have hypertension and symptomatic cardiovascular disease compared to subjects with an AAI of 0.90 or higher (Chapter 2).

In Chapter 3 we examined atherosclerotic risk factors for PAD. Determinants strongly and independently associated with PAD were age ≥ 75 years (odds ratio (OR) 1.2; 95% CI: 1.0-1.6), fibrinogen level (OR 1.5; 95% CI: 1.3-1.7), cigarette smoking (OR 2.8; 95% CI: 2.3-3.4), diabetes mellitus (OR 2.0; 95% CI: 1.6-2.5), and systolic blood pressure (OR 1.2; 95% CI: 1.1-1.2, per 10 mmHg rise). An inverse relation of HDL cholesterol level with PAD (OR 0.7; 95% CI: 0.5-0.8) was observed. Similar results were demonstrated for severe PAD (i.e. an AAI < 0.70). Separate analyses for men and women did not reveal differences in risk factors for PAD. The assessment of a wide range of atherosclerotic risk factors in the Rotterdam Study enabled us to quantify the relative importance of each factor as determinant for PAD. In total 56% of the occurrence of PAD was attributable to cardiovascular risk factors measured in this study; smoking accounted for the majority of cases (etiological fraction (EF): 18.1%). The results suggest that preventive management for PAD should be directed at systolic blood pressure, fibrinogen level, smoking, HDL cholesterol level, and diabetes mellitus.

In Chapter 4 the role of glucose and insulin in the progression of PAD in a sample of 965 participants of the Rotterdam Study was studied. The measurement of the AAI was repeated after approximately 2 years (range 0.6-5.1). Higher baseline glucose levels were associated with a decline of AAI (coefficient of linear regression -0.014 per standard deviation (SD) per year (95% CI: -0.023 to -0.006, adjusted for age and gender), whereas baseline insulin level showed no association. The same pattern was found for the incidence of PAD: the relative risk (RR) of glucose was 1.2 per SD (95% CI: 1.1-1.4) and of insulin 1.0 per SD (95% CI: 0.8-1.2). Diabetes mellitus at baseline was associated with an increased incidence of PAD: RR 1.9 (95% CI: 1.2-3.3). The associations were essentially the same in men and women, and remained similar after further adjustment for baseline AAI, use of antihypertensive medication, or body mass index. These results indicate that circulating insulin levels do not play a role in the progression of PAD in the elderly and underline the importance of elevated serum glucose as a risk factor for atherosclerotic disease.

During a mean follow-up of 6.5 years (range 5.1 to 9.5) we determined the age- and sex-specific incidence of PAD and intermittent claudication in 7,591 subjects (Chapter 5). The incidence of PAD was 22.7 per 1,000 person years (95% CI: 20.4-25.1) and very similar in men and women. The incidence of intermittent claudication was 2.8 per 1,000 person years (95% CI: 2.2-3.6); 4.4 per 1,000 person years in men and 1.7 per 1,000 person years in women. Of those with PAD and no complaints of intermittent claudication at baseline, 4.7% reported symptoms of intermittent claudication at the end of follow-up (9.6% in men, 2.4% in women). The risk factors which were strongest associated with incident PAD were older age (RR 1.6), male

gender (RR 1.5), smoking (RR 1.5), diabetes mellitus (RR 2.7), fibrinogen level ≥3.5 g/l (RR 1.9), and systolic blood pressure (RR 1.1).

Because data on the incidence and management of intermittent claudication in primary care are scarce, we studied the occurence and management of intermittent claudication in general practice in the Netherlands (Chapter 6). We used data from the Dutch National Survey of Morbidity and Interventions in General Practice (NIVEL), in which 161 GPs registered every contact between patient and practice. All episodes registered with the ICPC-code K92 (intermittent claudication) were selected and all available information on the GPs' management of the patients was studied. The overall incidence rate of intermittent claudication was 6.4 per 1,000 person years (95% CI: 5.3-7.7). The incidence rate increased from 4.0 per 1,000 person years in men aged 55-59 to 12.9 per 1,000 person years in men aged over 85, and for women in the same age categories from 3.3 per 1,000 person years to 8.2 per 1,000 person years, respectively. Of the 117 incident cases of intermittent claudication, 43 (37%) were referred to a specialist. In 55 cases (47%) drugs were prescribed by the GP and in 101 cases (86%) the GP gave lifestyle advice, notably pertaining to exercise and cessation of smoking.

In Chapter 7, the prognosis of PAD and the prognostic value of the AAI in the population at large were studied during a mean follow-up period of 3.7 years (range 0.1-6.2). Compared to subjects with an AAI ≥0.90 and no intermittent claudication, those with both intermittent claudication and an AAI<0.90 had an age- and sex-adjusted twofold risk for all-cause mortality (hazard ratio (HR) 2.3; 95% CI: 1.5-3.6). In those with an AAI<0.90 and no intermittent claudication the HR was 1.8 (95% CI: 1.5-2.1), while in participants with an AAI ≥0.90 and complaints of intermittent claudication the HR was 1.4 (95% CI: 0.6-3.3). Additional adjustment for the presence of myocardial infarction, stroke, smoking, and diabetes mellitus at baseline only slightly reduced these HRs. The same pattern was observed for the risk of cardiovascular mortality and non-fatal cardiovascular disease, both after adjustment for age and sex, and additional adjustment for the other possible confounders. A clear increase of the risk for all-cause and cardiovascular mortality with a decrease of the AAI was observed.

Early detection of PAD can be of help in preventing cardiovascular disease, because patients with PAD are at an increased risk, even if they are asymptomatic. Since massive screening for PAD is expensive and time consuming, we assessed whether preselection of subjects with an increased probability of having PAD would be possible (Chapter 8). Three risk functions (based on cardiovascular risk indicators) were developed to assess whether application of these functions could decrease the number of subjects that require screening (i.e. measurement of the AAI), while still detecting most subjects with PAD. The first risk function was based on age and gender alone, in the

second age and gender were combined with findings from a short medical questionnaire, and the third also included measurements such as blood pressure and serum cholesterol. In all analyses the risk function based on age and gender alone seemed preferable (26-57% of all subjects would be selected for screening, while 54-78% of those with PAD would be detected). Addition of other risk indicators for the disease in the risk function did not improve the effectiveness of the screening.

In the Chapter 9 the results of the studies are discussed and recommendations for future studies are given. Because PAD is common among the elderly, future research could be focused on both the etiology of PAD and possible intervention schemes to guide prevention of early stages of PAD or possible future cardiovascular events. More research into the role of hematological factors, genetic risk factors, and inflammatory agents in atherogenesis and PAD is needed. Also, possible protective factors for the development of PAD deserve further study. In addition, the evaluation of means of prevention of PAD (lifestyle modification, exercise therapy and interventions with antiplatelet or lipid-lowering agents) deserve attention. To detect those 'at risk' a measure of subclinical PAD, such as the AAI, is necessary. The use of the AAI as risk indicator in cardiovascular screening and risk profiling needs to be advocated to accept the challenge of preventing or reducing cardiovascular events in the elderly.

Chapter 11

Samenvatting

Samenvatting

Zowel in Nederland, alsook in de meeste westerse landen, is er een afname in de afgelopen twintig jaar van hart- en vaatziekten sterfte ten gevolge van atherosclerose, maar is er een duidelijke toename van hart- en vaatziekten morbiditeit, met name bij ouderen. Atherosclerose is de meeste voorkomende oorzaak van perifeer arterieel vaatlijden (PAV), een chronische obstructieve aandoening van het arteriële systeem distaal van de aorta bifurcatie. In een vroeg stadium is PAV asymptomatisch, maar in latere stadia kan zich dit uiten in klachten van claudicatio intermittens. PAV is een belangrijk gezondheidsprobleem bij ouderen omdat de prevalentie sterk toeneemt bij het stijgen van de leeftijd en personen met PAV vaker fatale en niet-fatale hart- en vaatziekten, zoals een myocard infarct of een beroerte, doormaken. Vergeleken met andere uitingen van atherosclerose, zoals coronaire hartziekten (CHZ), hebben zich maar weinig prospectieve cohortstudies gericht op de epidemiologie van PAV. Met name studies betreffende de incidentie en prognose (en hun determinanten) van PAV zijn zeldzaam (Hoofdstuk 1).

Het doel van het onderzoek dat in dit proefschrift beschreven wordt behelst het verder onderzoeken van de klinische epidemiologie van PAV bij ouderen. Resultaten die in dit proefschrift beschreven worden zijn gebaseerd op de eerste fase (1990-1993) en follow-up fases (eerste vervolg: 1993-1995, en tweede vervolg: 1997-1999) van de 'Rotterdam Study', een prospectief follow-up onderzoek bij mannen en vrouwen van 55 jaar en ouder, wonend in de Rotterdamse wijk Ommoord. De eerste fase van de studie kende een respons van 78% (n=7.983; 3.105 mannen en 4.878 vrouwen). De aanwezigheid van PAV en claudicatio intermittens werden respectievelijk vastgesteld door bepaling van de enkel-arm index (EAI), en aan de hand van de WHO/Rose-vragenlijst. PAV werd gedefinieerd als een EAI kleiner dan 0,90 aan tenminste één been. Klinische follow-up data betreffende fatale en niet fatale eindpunten werden verzameld via de huisartsen die werkzaam waren in het onderzoeksgebied van de 'Rotterdam Study' middels een directe verbinding tussen de geautomatiseerde huisartsenbestanden en het computersysteem van de 'Rotterdam Study'.
De leeftijds- en geslachtsspecifieke prevalentie van PAV was 19,1% (95% betrouwbaarheidsinterval (BI): 18,1-20,0); 16,9% bij mannen en 20,5% bij vrouwen (Hoofdstuk 2). Symptomen van claudicatio intermittens werden gemeld door 1,6% (95% BI: 1,3-1,9) van de deelnemers (2,2% van de mannen en 1,2% van de vrouwen). Van degenen met PAV meldden 6,3% tevens symptomen van claudicatio intermittens (8,7% van de mannen; 4,9% van de vrouwen), daarentegen hadden 68,9% van degenen met claudicatio intermittens een EAI lager dan 0,90. Personen met een EAI lager dan 0,90

bleken vaker rokers te zijn en hypertensie en symptomatische hart- en vaatziekten te hebben in vergelijking met personen met een EAI van 0,90 of hoger (Hoofstuk 2).

In Hoofdstuk 3 onderzochten wij atherosclerotische risicofactoren voor PAV. De belangrijkste, en onafhankelijk gerelateerde determinanten voor PAV waren een leeftijd van 75 jaar of ouder (odds ratio (OR) 1,2; 95% BI: 1,0-1,6), serum fibrinogeen niveau (OR 1,5; 95% BI: 1,3-1,7), roken (OR 2,8; 95% BI: 2,3-3,4), diabetes mellitus (OR 2,0; 95% BI: 1,6-2,5), en systolische bloeddruk (OR 1,2; 95% BI: 1,1-1,2). Er werd een negatieve relatie met HDL-cholesterol niveau en PAV (OR 0,7; 95% BI: 0,5-0,8) gevonden. Vergelijkbare resultaten werden aangetoond voor 'ernstige' PAV (d.i. een EAI < 0,70). Aparte analyses voor mannen en vrouwen lieten geen verschillen in risicofactoren voor PAV zien. De bepaling van een groot scala aan atherosclerotische risicofactoren in de 'Rotterdam Study' stelde ons in staat de relatieve importantie van iedere factor als determinant van PAV te kwantificeren. In totaal 56% van het vóórkomen van PAV was toe te schrijven aan cardiovasculaire risicofactoren die in onze studie bepaald waren; roken verklaarde de meerderheid van de gevallen (etiologische fractie (EF): 18,1%). De resultaten suggereren dat preventief management met betrekking tot PAV gericht zou moeten worden op systolische bloeddruk, fibrinogeen niveau, roken, HDL-cholesterol niveau, en diabetes mellitus.

In Hoofdstuk 4 werd de rol van glucose en insuline met betrekking tot de progressie van PAV bestudeerd in een representatieve steekproef van 965 deelnemers van de 'Rotterdam Study'. De meting van de EAI werd gemiddeld na 2 jaar (0,6-5,1 jaar) herhaald. Hogere glucose niveaus in de eerste fase waren gecorreleerd met een afname van de EAI (lineare regressiecoëfficiënt: -0,014 per standaard deviatie (SD) per jaar (95% BI: -0,023 tot -0,006; gecorrigeerd voor leeftijd en geslacht), terwijl insuline niveaus in de eerste fase geen verband toonden. Hetzelfde patroon werd gevonden voor de incidentie van PAV: het relatieve risico (RR) van glucose was 1,2 per SD (95% BI: 1,1-1,4) en van insuline 1,0 per SD (95% BI: 0,8-1,2). Diabetes mellitus in de eerste fase was gecorreleerd met een toegenomen incidentie van PAV: RR 1,9 (95% BI: 1,2-3,3). De correlaties waren wezenlijk hetzelfde bij mannen en vrouwen, en bleven gelijk na verdere correctie voor de EAI in de eerste fase, gebruik van antihypertensiva, of Quetelet-index. Deze resultaten geven aan dat het circulerende insuline niveau geen rol speelt bij de progressie van PAV bij ouderen, en onderstrepen de importantie van een verhoogd serum glucose niveau als risico factor voor atherosclerotische aandoeningen.

Na een gemiddelde follow-up duur van 6,5 jaar (5,1 tot 9,5 jaar) bepaalden we de leeftijds- en geslachtsspecifieke incidentie van PAV en claudicatio intermittens bij 7.591 deelnemers (Hoofdstuk 5). De incidentie van PAV was 22,7 per 1.000 persoonsjaren (pj) (95% BI: 20,4-25,1) en vergelijkbaar bij zowel mannen als vrouwen.

De incidentie van claudicatio intermittens was 2,8 per 1.000 pj (95% BI: 2,2-3,6); 4,4 per 1.000 pj bij mannen en 1,7 per 1.000 pj bij vrouwen. Van degenen met PAV zónder klachten van claudicatio intermittens in de eerste fase meldden 4,7% symptomen van claudicatio intermittens aan het einde van de follow-up periode (9,6% van de mannen en 2,4% van de vrouwen). De risicofactoren met de beste correlatie met incidente PAV waren: oudere leeftijd (RR 1,6), mannelijk geslacht (RR 1,5), roken (RR 1,5), diabetes mellitus (RR 2,7), fibrinogeen niveau ≥3.5 g/l (RR 1,9), en systolische bloeddruk (RR 1,1).

Omdat er weinig gegevens betreffende incidentie en behandeling van claudicatio intermittens in de huisartsenpraktijk bekend zijn, bestudeerden wij het vóórkomen en de behandeling van claudicatio intermittens in de huisartsenpraktijk in Nederland (Hoofdstuk 6). Wij maakten gebruik van data van de Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk (NIVEL), waarin 161 huisartsen elk praktijkconsult registreerden gedurende 3 maanden. Elk consult dat gecodeerd werd met de ICPC-code K92 (claudicatio intermittens) werd geselecteerd en alle beschikbare informatie betreffende de behandeling van de huisarts bestudeerd. De incidentie van claudicatio intermittens was 6,4 per 1.000 pj (95% BI: 5,3-7,7). De incidentie nam toe van 4,0 per 1.000 pj bij mannen in de leeftijd van 55-59 jaar tot 12,9 per 1.000 pj bij mannen van 85 jaar en ouder, en bij vrouwen in dezelfde leeftijdscategorieën van 3,3 per 1.000 pj tot respectievelijk 8,2 per 1.000 pj. Van de 117 incidente gevallen van claudicatio intermittens werden 43 (37%) verwezen naar een specialist. Bij 55 gevallen (47%) werden medicijnen voorgeschreven door de huisarts, en bij 101 gevallen (86%) gaf de huisarts advies betreffende leefregels, zoals meer beweging en stoppen met roken.

In Hoofdstuk 7 werd de prognose van PAV en de prognostische waarde van de EAI in de algehele bevolking bestudeerd gedurende een gemiddelde follow-up periode van 3,7 jaar (0,1-6,2 jaar). Vergeleken met personen met een EAI ≥0.90 zónder klachten van claudicatio intermittens hadden degenen met zowel claudicatio intermittens als een EAI<0.90 een twee keer zo groot risico (gecorrigeerd voor leeftijd en geslacht) voor algehele sterfte (hazard ratio (HR) 2,3; 95% BI: 1,5-3,6). Voor degenen met een EAI<0.90 zónder claudicatio intermittens was de HR 1,8 (95% BI: 1,5-2,1), terwijl deelnemers met een EAI ≥0.90 en klachten van claudicatio intermittens een HR van 1,4 (95% BI: 0,6-3,3) hadden. Verdere correctie voor een doorgemaakt myocard infarct of beroerte, roken, en aanwezige diabetes mellitus verkleinden deze HR's slechts in geringe mate. Hetzelfde patroon was waarneembaar voor het risico voor hart- en vaatziektensterfte en niet-fatale hart- en vaatziekten, beide na correctie voor leeftijd en geslacht, en verdere correctie voor de andere mogelijke confounders. Er werd een duidelijke toename voor het risico voor algehele en hart- en vaatziektensterfte met een

afnemende EAI geconstateerd.

Vroege detectie van PAV kan van nut zijn bij preventie van hart- en vaatziekten omdat patiënten met PAV een verhoogd risico hierop hebben, zelfs als ze asymptomatisch zijn. Omdat algehele screening voor PAV te duur is en teveel tijd kost, hebben we bepaald of een voorselectie van personen met een verhoogd risico op het krijgen van PAV mogelijk is (Hoofdstuk 8). Er werden drie risicofuncties (gebaseerd op hart- en vaatziektenrisico indicatoren) ontwikkeld om te bepalen of toepassing van deze risicofuncties het aantal te screenen (door middel van de EAI) personen kon terugdringen waarbij toch nog de meeste personen met PAV worden opgespoord. De eerste risicofunctie was gebaseerd op alleen leeftijd en geslacht, in de tweede was dit gecombineerd met anamnestische gegevens, en de derde functie bevatte hiernaast ook metingen zoals bloeddruk en cholesterol niveau. In alle analyses lijkt de risicofunctie gebaseerd op alleen leeftijd en geslacht te prevaleren (26-57% van alle personen zouden geselecteerd worden voor de screening, terwijl 54-78% van degenen met PAV zouden worden opgespoord). Toevoeging van andere risicoindicatoren voor PAV in de risicofunctie verbeterde de effectiviteit van de screening niet.

In Hoofdstuk 9 worden de resultaten van de studies bediscussieerd en worden aanbevelingen voor toekomstige studies gegeven. Omdat PAV vaak voorkomt bij ouderen zou toekomstig onderzoek zich kunnen richten op zowel de etiologie van PAV als mogelijkheden tot interventie leidend tot voorkoming van vroege stadia van PAV of mogelijke toekomstige hart- en vaatziekten. Meer onderzoek naar de rol van haematologische factoren, genetische risicofactoren, en ontstekingsfactoren bij de atherogenese PAV is noodzakelijk. Ook de rol van mogelijke beschermende factoren bij de ontwikkeling van PAV verdienen verdere studie. Verder verdient de evaluatie van preventieve maatregelen tegen PAV (zoals leefregels, looptraining, en interventies met plaatjesaggregatieremmers of cholesterolverlagende middelen) aandacht. Om degenen met verhoogd risico op te sporen is een 'maat voor subklinische PAV', zoals de EAI, nodig. Het gebruik van de EAI als risicoindicator bij hart- en vaatziektenscreening en risicoprofilering moet verder bepleit worden om de uitdaging van preventie of reductie van hart- en vaatziekten bij ouderen, aan te kunnen nemen.

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Curriculum Vitae

Wouter Theodoor Meijer was born in Zaandam, the Netherlands, on February 26, 1963. After secondary school he attended art academy, to become a sculptor. During the illness of both his parents he realized that the abstractions of art offered little help in understanding disease. He attended medical school at Erasmus University, Rotterdam, and received his MD in 1995. In 1996 the work described in this PhD-thesis was initiated at the Department of Epidemiology & Biostatistics (head: prof.dr. A. Hofman) and the Department of General Practice (head: prof.dr. S. Thomas), Erasmus University Medical School, Rotterdam. During his PhD-fellowship he obtained a master's degree in clinical epidemiology at the Netherlands Institute for Health Sciences (NIHES).
In October 1999 he started his training as a radiologist at the University Hospital Rotterdam 'Dijkzigt' (head: prof.dr. G.P. Krestin).