

Determinants of Peripheral Arterial Disease in the Elderly

The Rotterdam Study

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Objective: To examine which atherosclerotic risk factors are determinants for peripheral arterial disease (PAD), we performed a population-based study in 6450 subjects (40% men, 60% women) aged 55 years and older.

Methods: The presence of PAD was assessed by measuring the ankle-arm systolic blood pressure index (AAI); PAD was considered present if the AAI was lower than 0.90 in either leg. In addition, a threshold AAI of 0.70 in either leg defined severe PAD.

Results: Determinants strongly and independently associated with PAD were age of at least 75 years (odds ratio [OR], 1.2; 95% confidence interval [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). An inverse relation of high-

density lipoprotein cholesterol level with PAD (OR, 0.7; 95% CI, 0.5-0.8) was found. Similar results were demonstrated for severe PAD. Separate analyses for men and women did not demonstrate differences in risk factors for PAD.

Conclusions: Assessment of a wide range of atherosclerotic risk factors enabled us to quantify the relative importance of each factor as determinant for PAD. In total, 69% of the occurrence of PAD is attributable to cardiovascular risk factors measured in our study; smoking accounted for most (etiologic fraction, 18.1%). The results suggest that preventive management of PAD should be directed at systolic blood pressure, fibrinogen level, smoking, high-density lipoprotein cholesterol level, and diabetes mellitus.

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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} Peripheral arterial disease is a manifestation of generalized atherosclerosis, and life expectancy in patients with PAD is reduced compared with subjects without PAD. This is mainly attributable to an increased incidence of cardiovascular disease³⁻⁵ 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 reversible and irreversible categories. Reversible risk factors for PAD include cigarette smoking and hypertension, whereas nonreversible risk factors include age, sex, and genetic factors.⁹⁻¹³

The purpose of our study was to assess which determinants are involved in the

etiology of PAD, and to what extent known atherosclerotic risk factors are involved, in a large population-based setting.

RESULTS

General characteristics of the study population are given in **Table 1**. When defined as an AAI of less than 0.90, PAD was present in 19% (95% CI, 18%-20%) of all participants; when defined as an AAI of less than 0.70, PAD was present in 8% (95% CI, 7%-9%) of all participants. After adjusting for age, no major differences in prevalence 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**).

The age- and sex-adjusted ORs and the multivariate ORs (with 95% CIs) of potential determinants of PAD (defined as AAI <0.90) and of severe PAD (defined as AAI <0.70) are shown in **Table 2** and **Table 3**, respectively. Only determinants that show an association with PAD are given.

Determinants with a strong positive association with PAD were age older than 75 years, fibrinogen level, current smok-

PATIENTS AND METHODS

Our 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 AAI have been described previously.¹⁵ Briefly, in 6450 participants (2589 men and 3861 women) aged 55 years or older living in the suburb of Ommoord in Rotterdam, the Netherlands, the ratio of the systolic blood pressure at the ankle (measured by means of an 8-MHz continuous-wave Doppler probe at the posterior tibial artery) and 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 AAIs was used in the analysis. We measured the arm blood pressures in the right and left arm, and subjects with large left-right differences (a possible sign of vascular disease in the brachial tree) were excluded from the analyses because this could affect the reliability of the AAI. Also, subjects with an AAI of greater than 1.50 were excluded, since an extremely high AAI usually reflects arterial rigidity, preventing arterial compression and leading to spuriously high ankle blood pressure values.

In agreement with the approach followed by Fowkes et al⁷ and by Schroll and Munck,¹² PAD was considered present when the AAI was lower than 0.90 in at least 1 leg, a threshold value used in most current studies.^{5,7,12,16,17} In addition to this conventional threshold value for PAD, we also used an AAI of 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 140 mm Hg or higher, or a diastolic blood pressure of 90 mm Hg or higher, or current use of antihypertensive drugs for the indication of hypertension.¹⁹ Diabetes mellitus was defined as the current use of antidiabetic drugs or a random or postload serum glucose level of greater than 11.0 mmol/L (198 mg/dL) 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 semiquantitative food frequency questionnaire. One drink is roughly equivalent to 10 g of alcohol. Venipuncture was performed, applying minimal stasis and using a 21-gauge butterfly needle. Samples were collected into siliconized blood-collection

tubes (Vacutainer; Becton Dickinson & Co, Mylan, France) containing 3.8% trisodium citrate and centrifuged for 10 minutes at 1600g at 4°C. Plasma was separated, centrifuged for 10 minutes at 10000g at 4°C, and stored at -80°C before assay. Serum total cholesterol level was determined using an automated enzymatic procedure.²² Serum high-density lipoprotein (HDL) cholesterol level 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 a sensitive thromboplastic preparation from human placenta (Thromborel S; Dade Behring Inc, Deerfield, Ill) as reagent on an automated coagulation laboratory coagulometer (ACL 300; Instrumentation Laboratory, Jsselstein, the Netherlands).²⁵ This method correlates well with the frequently used method described by von Clauss.²⁶

Total homocysteine level was measured as a fluorescent derivative using high-pressure liquid chromatography according to the method of Araki and Sako,²⁷ as modified by Ubbink et al.²⁸ Data on total homocysteine levels were available in 630 randomly selected subjects participating in our study. White blood cell count (leukocytes) and hematocrit level were quantified using a counter (Coulter Electronics, Inc; Fullerton, Calif). Height and weight were measured, and the body mass index (weight in kilograms divided by the square of height in meters) was calculated. Body fat distribution was assessed by the ratio of waist and hip circumferences.

Age- and sex-adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using a logistic regression model, with the presence of PAD as the dependent variable, for threshold AAIs of 0.90 and 0.70. Next, multivariate ORs with 95% CIs 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 etiologic fraction was calculated, using the following formula:

$$\text{Etiologic Fraction} = \text{Case Fraction} \times [(\text{RR} - 1) / \text{RR}]$$

where the relative risk (RR) is taken as the OR of the risk indicator resulting from the multiple logistic regression analyses, and the case fraction is the prevalence of the risk indicator in subjects with PAD.²⁹ Analyses were performed using commercially available software (BMDP Statistical Software, Inc, Los Angeles, Calif).

ing of cigarettes, systolic blood pressure (per 10-mm Hg rise), 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 nonsignificant associations with PAD were found for total cholesterol level, leukocyte count, total homocysteine level, and alcohol intake of more than 20 g/d.

In the analyses with both threshold values of the AAI (AAI <0.90 vs \geq 0.90 and AAI <0.70 vs \geq 0.70), there was a clear inverse relation with HDL cholesterol level, ie, a higher HDL cholesterol level protects against PAD (Table 2). All other investigated determinants in this study did not show a clear association with PAD. Similar re-

sults for PAD with a threshold value of AAI of less than 0.70 were found (Table 3), and separate analyses for men and women did not reveal differences in risk factors for a threshold AAI of 0.90 or 0.70.

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 older than 75 years explains 11% of the occurrence of PAD. Reversible risk factors for PAD, such as hypertension, a serum total cholesterol level of 6.2 mmol/L or higher (\geq 112 mg/dL), a serum HDL cholesterol level of lower than 0.9 mmol/L (<35 mg/dL), current and former smoking, a plasma fibrinogen level of 10.3 μ mol/L or higher, and diabetes mellitus con-

Table 1. General Characteristics of 6450 Men and Women Aged 55 Years or Older in Whom Presence of PAD Was Assessed*

Characteristic	Men (n = 2589)	Women (n = 3861)
Age, y	68.3 (8.4)	70.3 (9.7)
Body mass index†	25.7 (3.7)	26.7 (4.1)
Waist-to-hip ratio	0.96 (0.07)	0.87 (0.09)
Systolic blood pressure, mm Hg	139 (22)	140 (23)
Diastolic blood pressure, mm Hg	75 (12)	73 (12)
Hypertension, %‡	49.8	54.8
Intermittent claudication, %§	2.1	1.4
Serum total cholesterol, mmol/L	6.3 (1.2)	6.8 (1.2)
Serum HDL cholesterol, mmol/L	1.2 (0.3)	1.4 (0.4)
Plasma fibrinogen, µmol/L	7.9 (2.1)¶	8.2 (2.1)¶
Leukocytes, ×10 ⁹ /L	6.8 (1.9)	6.6 (2.1)
Hematocrit	0.43 (0.04)	0.40 (0.04)
Total homocysteine, µmol/L	15.7 (4.3)#	14.5 (4.4)#
Smoking status, %		
Current	24.2	17.3
Former	59.3	27.8
Alcohol intake, d	16.5 (18.7)	6.1 (10.1)
Diabetes mellitus, %	7.6	8.5

*Unless otherwise indicated, data are given as mean (SD). PAD indicates peripheral arterial disease; HDL, high-density lipoprotein.

†Calculated as weight in kilograms divided by the square of height in meters.

‡Defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or current use of antihypertensive drugs for the indication of hypertension.¹⁹

§According to the criteria of the World Health Organization (Rose questionnaire).³⁰

||To obtain milligrams per deciliter, divide by 0.02586.

¶Data available from first 1000 men and first 1700 women participating in the Rotterdam Study.

#Data available from a random sample of 630 men and women participating in the Rotterdam Study.

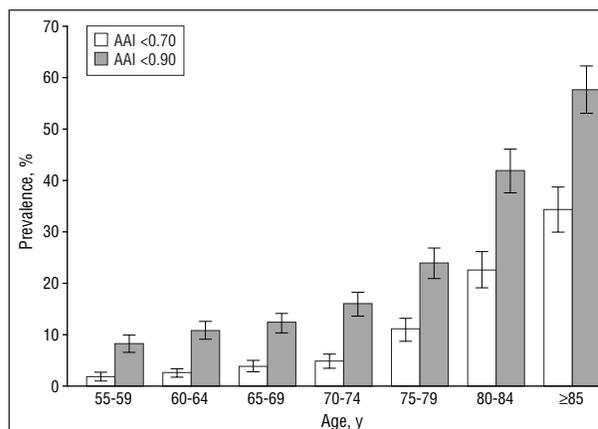
tribute to 58% of all cases of PAD. In total, 69% of the occurrence of PAD in this study is accounted for, which leaves 31% of the etiology of PAD unexplained by the determinants considered in our study.

COMMENT

In our large population-based study, we were able to assess several possible determinants of PAD. Using a threshold AAI 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. Calculating the etiologic fraction for the determinants associated with PAD explained almost 70% of the occurrence of PAD in our study.

Our findings of a positive association between PAD and age, smoking, fibrinogen level, and diabetes mellitus are consistent with previous findings.^{5-7,12,32-40} Although most previous studies assessed these associations separately, 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.⁴⁰ The positive association of systolic blood



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 of less than 0.70 or of less than 0.90. Data are given as mean (SD).

Table 2. Potential Determinants of PAD*

Determinant	Odds Ratio (95% Confidence Interval)	
	Age and Sex Adjusted	Multivariate
Age ≥75 y	1.22 (0.96-1.55)	1.74 (0.97-3.11)
Systolic blood pressure per 10-mm Hg rise	1.18 (1.15-1.22)	1.30 (1.18-1.44)
Hypertension	1.92 (1.67-2.21)	1.32 (1.07-1.64)
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, µmol/L†	1.49 (1.29-1.72)	1.46 (1.10-1.93)
Leukocytes, ×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 status		
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 g/d	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)

*Calculated as age- and sex-adjusted odds ratios, and multivariate odds ratios with their 95% confidence intervals, for subjects with an ankle-arm systolic blood pressure index (AAI) < 0.90 and subjects with an AAI ≥ 0.90. Only determinants that showed a statistically significant association with peripheral arterial disease (PAD) are shown in the table. HDL indicates high-density lipoprotein. The definition for hypertension is given in the third footnote to Table 1.

†Data available from first 1000 men and first 1700 women participating in the Rotterdam Study.

‡Data available from a random sample of 630 men and women participating in the Rotterdam Study.

pressure, total cholesterol level, leukocyte count, and alcohol intake and the inverse association of HDL cholesterol level with PAD are also consistent with findings in other studies.* We did not find an association between hyperhomocyst(e)inemia and PAD, in contrast to several earlier studies,⁴⁶⁻⁴⁹ but this may be attributable to the older population (mean age, 67.8 years) with homocysteine data in our study, or the relatively small random sample.

When using a model²⁹ to assess the prevalence of the determinants among subjects with PAD (case frac-

*References 5, 10, 12, 13, 33, 34, 39, 41-45.

Table 3. Potential Determinants of Severe PAD*

Determinant	Odds Ratio (95% Confidence Interval)	
	Age and Sex Adjusted	Multivariate
Age ≥ 75 y	1.46 (1.03-2.07)	1.08 (1.01-1.15)
Systolic blood pressure per 10-mm Hg rise	1.18 (1.13-1.23)	1.34 (1.18-1.53)
Hypertension	1.88 (1.52-2.31)	1.39 (1.01-1.93)
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, $\mu\text{mol/L}\ddagger$	1.63 (1.35-1.97)	1.34 (0.90-2.01)
Leukocytes, $\times 10^9/\text{L}$	1.05 (1.01-1.10)	1.04 (0.91-1.18)
Total homocysteine, $\mu\text{mol/L}\ddagger$	1.04 (0.96-1.13)	1.05 (0.92-1.18)
Smoking status		
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 g/d	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)

*Calculated as age- and sex-adjusted odds ratios, and multivariate odds ratios with their 95% confidence intervals, for subjects with an ankle-arm systolic blood pressure index (AAI) < 0.70 and subjects with an AAI ≥ 0.70 . Only determinants that showed a statistically significant association with peripheral arterial disease (PAD) are shown in the table. HDL indicates high-density lipoprotein. The definition for hypertension is given in the third footnote to Table 1.

†Data available from first 1000 men and first 1700 women participating in the Rotterdam Study.

‡Data available from a random sample of 630 men and women participating in the Rotterdam Study.

tion), and the proportion of PAD that may be attributed to the studied determinants (etiologic fraction), we can account for 69% of the occurrence of PAD in our study. This finding suggests that more research is needed to identify additional factors involved in the etiology of PAD. Alternatively, however, the 31% of the presence of PAD not accounted for could be explained in part by limitations in the assessment of presence and severity of PAD.

We used the AAI as a noninvasive measure of PAD. The threshold AAI of 0.90 that we used is up to 95% sensitive and about 100% specific in detecting disease with positive angiographic findings⁵⁰ and is related to the severity of the disease.⁵¹ Furthermore, Fowkes et al⁵² found a close relationship between the AAI and the results of duplex scanning of the major arteries of the leg. 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.

CONCLUSIONS

Although several risk factors show an association with PAD, determinants such as older age, hypertension, cholesterol level, smoking, fibrinogen level, and diabetes mellitus contribute to about 70% of all causes of PAD in our study population (Table 4). More research needs to be done to disclose further the etiology of PAD. Our results suggest that preventive management of PAD should be directed at systolic blood pressure, fibrinogen level, total and HDL cholesterol levels, smoking, and diabetes mellitus.

Table 4. Case Fraction and Etiologic Fraction of Different Risk Factors for PAD*

Risk Indicator	Case Fraction, %	Etiologic Fraction, %
Age ≥ 75 y	25.8	11.0
Hypertension†	69.2	17.0
Serum total cholesterol ≥ 6.2 mmol/L‡	57.5	6.7
Serum HDL cholesterol < 0.9 mmol/L‡	14.3	2.5
Plasma fibrinogen ≥ 10.3 $\mu\text{mol/L}\S$	11.7	3.7
Smoking status		
Current	28.9	18.1
Former	32.1	4.2
Diabetes mellitus	11.4	5.4

*Case fraction indicates the prevalence of risk indicator among subjects with peripheral arterial disease (PAD), etiologic fraction, proportion of PAD that may be attributed to that risk factor. HDL indicates high-density lipoprotein.

†Defined by the guidelines of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.¹⁹

‡Defined by the guidelines of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.³¹ To obtain milligrams per deciliter, divide by 0.2586.

§Data available from 1000 men and first 1700 women participating in the Rotterdam Study.

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