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A clinical prediction model for the presence of peripheral arterial disease – the benefit of screening individuals before initiation of measurement of the ankle–brachial index: an observational study

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Abstract: Measurement of the ankle–brachial index (ABI) can provide important information about the presence of subclinical atherosclerosis. Performing the ABI in the overall population is not feasible, but it can be used in a selected population. A simple prediction rule could be of much use to estimate the risk of an abnormal ABI. This was designed as an observational study in the setting of 955 general practices in The Netherlands. A total of 7454 patients aged ≥ 55 years presenting with at least one vascular risk factor (smoking, hypertension, diabetes, and hypercholesterolemia) and no complaints of intermittent claudication were included. Patients were selected by the general practitioner during visiting hours and from medical records. Main outcome measures included the prevalence of PAD, defined as an ABI below 0.9, which was related to vascular risk factors using regression analyses on which the PREVALENT clinical prediction model was developed. The overall prevalence of PAD was 18.4%. Since the treatment of individuals with a history of coronary heart disease and cerebrovascular disease will not be influenced by the finding of asymptomatic PAD, these individuals were not taken into account for the development of the clinical prediction model. Analyses showed a significantly increased risk for PAD with increasing age, smoking, and hypertension. The clinical prediction model giving risk factor points per factor (age: 1 point per 5 years starting at 55 years; ever smoked: 2 points; currently smoking: 7 points; and hypertension: 3 points), showed a proportional increase of the PAD prevalence with each increasing risk profile (range: 7.0–40.6%). In conclusion, based on the PREVALENT clinical prediction model, the general practitioner is able to identify a high-risk population in which measurement of ABI is useful.

Key words: ankle–brachial index; asymptomatic; atherosclerosis; peripheral arterial disease; screening

Introduction

The clinical importance of early identification and treatment of (asymptomatic) peripheral arterial disease (PAD) has been increasingly acknowledged in

recent years.¹ The recent AHA/ACC guidelines for the management of patients with PAD states that early detection and treatment of PAD, particularly in the populations at risk, may prevent disability and save lives.² PAD is a common disorder in the general population with an estimated overall prevalence varying between 9% and 23% among people of 55 years or older. The majority of patients with PAD is asymptomatic, or has leg symptoms other than classical intermittent claudication and remains currently unidentified. Despite the absence of typical clinical complaints, the risk of cardiovascular morbidity and mortality is increased substantially (two- to threefold) in those asymptomatic patients with an ankle–brachial index (ABI) of 0.9 or less.^{3,4}

Clearly, in individuals at risk due to the presence of one or more vascular risk factors, the detection of asymptomatic PAD may cause a shift from primary prevention to secondary prevention, resulting in more rigorous treatment targets.² In a recent review, it has

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been suggested that the ABI should not be used as a generic screening test due to its low sensitivity to predict future cardiovascular outcomes.⁵ In contrast it should be applied in a focused manner, selecting individuals for whom the yield of this measurement can be expected to be highest.

General practitioners (GPs) play a key role in the recognition, diagnosis and treatment of PAD. When depending solely on the patient's history, an underestimate of the prevalence of PAD may occur, and asymptomatic individuals will not be recognized at all. In the populations at risk this may currently lead to inadequate prevention of cardiovascular events.⁶ Measurement of ABI is a tool to provide important information about subclinical atherosclerosis.⁷ One of the main barriers to implement ABI measurement in general practice appears to be the time constraints of the responsible physician.⁸ With the increasing workload of GPs an easy screening tool is needed to assess whether an ABI measurement is likely to be of clinical use.

The aim of the present study was to develop a clinical prediction model for a simple and quick assessment of the likelihood of the presence of an abnormal ABI in asymptomatic individuals. This clinical prediction model should be based on generally accepted vascular risk factors such as increasing age, sex, smoking, hypertension, diabetes mellitus, hypercholesterolemia, history of cardio- or cerebrovascular disease, and a family history of vascular disease.

Methods

Study population

This observational study was part of the larger PREVALENT study and was conducted from October 2002 to February 2005 among 955 general practices in The Netherlands. Individuals of 55 years of age and older, presenting with at least one vascular risk factor (e.g. smoking, hypertension, diabetes mellitus, and hypercholesterolemia), and no complaints of intermittent claudication, were asked to participate. Excluded were patients with PAD Fontaine stage III and IV. Patients during visiting hours and patients selected from medical records (based on the presence of vascular risk factors) were included by the GP. Informed consent was obtained from eligible patients.

Assessment of risk factors

The risk factors the GP was requested to record were smoking, diabetes mellitus, hypertension, hypercholesterolemia, body mass index, a family history of vascular disease, previous myocardial infarction, angina pectoris, prior angioplasty or coronary bypass surgery, and prior ischemic stroke. For data analyses these data were extracted from the patient file or assessed by the GP during the patient's visit.

Smoking behaviour was recorded as: never smokers, current smokers, and former smokers with a smoking history of at least 10 pack years. Diabetes mellitus was considered present if serum fasting glucose levels were higher than 6.0 mmol/l and/or if blood glucose lowering medication was prescribed. Adequately treated diabetes mellitus was defined as using blood glucose lowering medication and a serum fasting glucose level below 6.0 mmol/l. Fasting glucose was measured once. Hypertension was defined as the presence of a systolic blood pressure of 140 mmHg or higher, and/or a diastolic blood pressure of 90 mmHg or higher, and/or the use of medication for hypertension. Individuals using medication for hypertension with a systolic blood pressure below 140 mmHg and a diastolic blood pressure below 90 mmHg were considered to be adequately treated for hypertension. The arterial blood pressure was measured once. Hypercholesterolemia was defined as a serum total cholesterol of 5.0 mmol/l or higher and/or the use of cholesterol lowering medication, whereas sufficiently treated high cholesterol was considered in individuals receiving medication and with a total cholesterol level below 5.0 mmol/l. A family history of vascular disease was considered to be present if a first-grade relative had experienced a vascular event before the age of 60 years.

Assessment of the ABI

To measure the ABI, the systolic brachial blood pressure was measured by means of auscultation at both arms, after which the systolic blood pressures of both the dorsalis pedis and posterior tibial arteries were measured at the malleolar level by an 8 MHz Doppler measurement device in both legs. The ABI was calculated for each leg by dividing the highest systolic pressure in the ankle by the highest brachial systolic pressure.⁹ The ABI was measured by the GP or his/her practice assistant. PAD was defined when an abnormal ABI of less than 0.9 was determined in one or both legs.

Analyses

The primary outcome measurement in the PREVALENT study was the existence of PAD, which was defined when an abnormal ABI was determined in one or both legs. The cut-off point of 0.9 was used because it is used in the majority of the recent studies, and has been shown to have a mean sensitivity of approximately 80%¹⁰ and a specificity of 99% for angiographically documented PAD.¹¹ All patients with an ABI between 0.9 and 1.4 in both legs were defined as normal. Since there is uncertainty about the interpretation of a high ABI (71.4),¹² patients with an ABI above 1.4 in one or both legs and without PAD, as defined above, were excluded. This was to prevent underestimation of PAD prevalence.

The demographic and clinical characteristics of the asymptomatic individuals were compared among

participants with and without PAD using the Students' *t*-test for binary variables and the chi-square test for nominal variables.

The prevalence of PAD was related to risk factors using multivariate conditional logistic regression analyses. The beta coefficients that resulted from the regression analyses were converted into odds ratios (OR). Based on these ORs, a clinical prediction model was developed. Finally, the outcomes of this clinical prediction model were related to the presence of PAD.

Results

The study included 7977 individuals without complaints of intermittent claudication. Of these 7977 individuals, 458 (5.7%) were measured to have an ABI above 1.4 in one or both legs with no ABI measurement below 0.9 in the other leg. These 458 individuals were excluded from the analyses. In addition, the ankle pressure of either leg could not be obtained in 65 (0.8%) patients, leaving 7454 patients available for our analyses (Figure 1). The general demographics and clinical characteristics of this cohort are detailed in Table 1.

The overall prevalence of PAD in this asymptomatic population was 18.4%. Most vascular risk factors were statistically significantly more prevalent in patients with an abnormal ABI compared to those with a normal ABI. A significant difference between male and female patients was not determined. The prevalence of diabetes mellitus was also equally distributed between the participants with and without PAD.

Multivariate model

Using stepwise logistic regression analysis, gender, diabetes mellitus, hypercholesterolemia, a positive

family history, and the body mass index were consistently removed from or not included in the final model. Calculations using the final logistic model showed a significantly increased risk for PAD with increasing age (OR: 1.34 per 5 years; confidence interval (CI): 1.29–1.40), smoking behaviour, including ever smoked (OR: 1.4; CI: 1.2–1.6) and current smoking (OR: 2.9; CI: 2.2–4.0), the presence of hypertension (OR: 1.5; CI: 1.3–1.8), adequately treated hypertension (OR: 1.2; CI: 1.1–1.4), the presence of coronary heart disease (OR: 1.6; CI: 1.4–1.8), and the presence of cerebrovascular disease (OR: 1.3; CI: 1.1–1.6). Based on the assumption that the treatment of patients with a history of a cardiovascular or cerebrovascular event will not be influenced by the finding of asymptomatic PAD, the previously mentioned risk factors were not taken into account in the final clinical prediction model. To translate the OR to an easy clinical decision rule, an OR of 1 was taken as 0 risk factor points, increasing with 1 risk factor point per increase of the OR by approximately 0.25. In Table 2 the clinical prediction model is shown.

Prevalence of PAD in relation to the clinical decision rule

The prevalence of an abnormal ABI according to the clinical prediction model increases proportionately with this score. The prevalence of an abnormal ABI was 7.0% in the lowest and 40.6% in the highest category (Table 3).

Discussion

This study estimates the prevalence of asymptomatic PAD in general practice in a large cohort of a representative adult population in The Netherlands in whom at

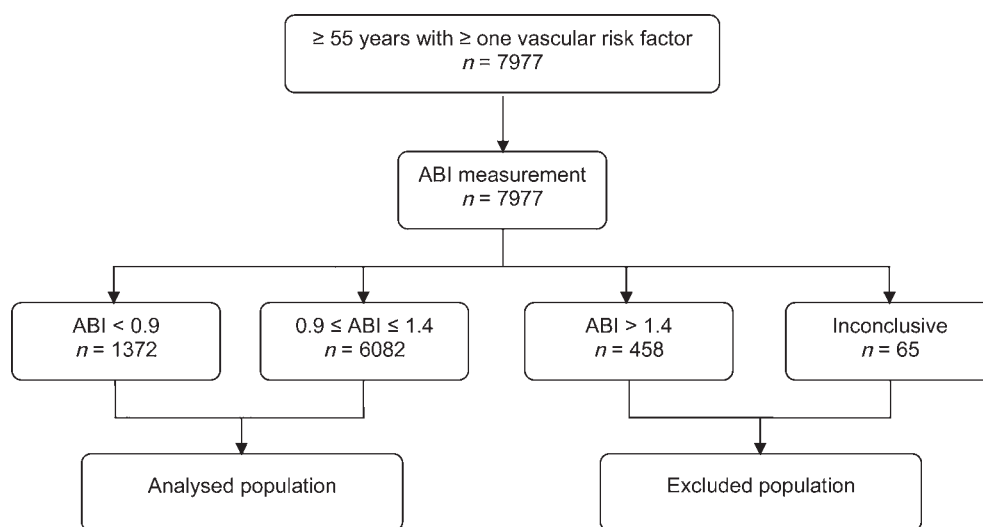


Figure 1 Inclusion schedule of analysed population.

Table 1 Demographic and clinical characteristics of the total population without complaints suggestive of intermittent claudication.

	Total population (n = 7454)	ABI < 0.9 (n = 1372)	0.9 ≤ ABI ≤ 1.4 (n = 6082)	p-value
Age, years: mean (SD)	67.6 (8.1)	70.3 (8.4)	67.0 (7.9)	p < 0.0001
Men: n (%)	3632 (48.7)	684 (49.9)	2948 (48.5)	NS
BMI: mean (SD)	27.7 (5.9)	27.2 (5.6)	27.8 (5.9)	p = 0.0009
Current smokers: n (%)	1847 (24.8)	475 (34.6)	1372 (22.6)	p < 0.0001
Ever smoked: n (%)	2520 (33.8)	444 (32.4)	2076 (34.1)	p < 0.0001
Never smoked: n (%)	2911 (39.1)	421 (30.7)	2490 (40.9)	p < 0.0001
Hypertension: n (%)	5910 (79.3)	1131 (82.4)	4779 (78.6)	p < 0.0001
Diabetes mellitus: n (%)	3263 (43.8)	619 (45.1)	2644 (43.5)	NS
Hypercholesterolemia: n (%)	4121 (55.3)	714 (52.0)	3407 (56.0)	p = 0.003
Family history: n (%)	2721 (36.5)	486 (35.4)	2235 (36.7)	NS
Coronary heart disease: n (%)	1299 (17.4)	334 (24.3)	965 (15.9)	p < 0.0001
Stroke or TIA: n (%)	576 (7.7)	140 (10.2)	436 (7.2)	p < 0.0001
Two risk factors present: n (%)	2736 (36.7)	475 (34.6)	2261 (37.2)	NS
Three or more risk factors present: n (%)	3272 (43.9)	664 (48.4)	2608 (42.9)	p < 0.0001

ABI, ankle-brachial index; SD, standard deviation; NS, not significant.

Table 2 Clinical prediction model according to the logistic regression.

Risk factor points	Age	Smoking behaviour	Hypertension
0	55–59 years n = 1490	Never smoked n = 2911	No hypertension n = 1349
+1	60–64 years n = 1413		Hypertension, adequately treated n = 1705
+2	65–69 years n = 1488	Ever smoked n = 2520	
+3	70–74 years n = 1426		Hypertension, not adequately treated n = 4205
+4	75–79 years n = 1047		
+5	80–84 years n = 457		
+6	≥ 85 years n = 133		
+7		Current smokers n = 1847	

least one vascular risk factor was present. The overall prevalence of asymptomatic PAD in this population determined by means of the detection of an abnormal ABI was 18.4%. This finding is consistent with other studies which have reported prevalence rates in asymptomatic patients with a PAD between 6% and 18%.^{13–16} A previous study has shown that approximately half of the patients with PAD in general practice clinics are asymptomatic.¹⁷

We demonstrate that the prevalence of asymptomatic PAD in our study was influenced by age, smoking behaviour, hypertension, and the presence of cardio- and cerebrovascular disease. Interestingly, despite the relatively large sample size, there was no statistically significant association between the

presence of diabetes mellitus alone and the presence of asymptomatic PAD. This finding is in contrast with earlier studies, which reported that asymptomatic PAD is more common in diabetic individuals.^{18,19}

We have developed a clinical prediction model that can be used to differentiate between patient groups from a lowest risk of 7.0% to a highest risk of 40.6% for the presence of PAD. Identification of asymptomatic PAD may identify those individuals who are at risk to develop vascular complications and who would otherwise not receive adequate risk factor management therapies.

When patients with a score above seven points are selected for an ABI measurement, four patients have to be tested to identify one asymptomatic patient with

Table 3 Prevalence of PAD according to the clinical prediction model in asymptomatic individuals.

Score	Prevalence (n)	ABI < 0.9 n (%)
0–3	1202	84 (7.0)
4	706	84 (11.9)
5	924	134 (14.5)
6	865	151 (17.5)
7	920	178 (19.3)
8	722	170 (23.5)
9	448	116 (25.9)
10	470	114 (24.3)
11	331	83 (25.1)
12	241	75 (31.1)
≥13	271	110 (40.6)

*ABI, ankle–brachial index.

PAD. Since this seems to be feasible in clinical practice, it can be recommended to screen this population. Based on the data of the current survey, we identified several risk profiles which may obtain a score of seven points or higher. For example, current smoking as a single risk factor satisfies a score of seven, independent of age, while former smokers will only obtain this level when 65 years or older, and with the presence of non-adequately treated hypertension.

Clinical implications

The status of current smoking was determined to have a five times greater effect on the presence of asymptomatic PAD compared to a history of smoking. This is comparable with the results of previous studies showing that smoking cessation significantly reduces the prevalence of symptomatic PAD and cardiovascular complications.^{20,21}

Hypertension increased the prediction of the presence of asymptomatic PAD by 50% compared to no hypertension, which is comparable with earlier reports.²² However, adequate treatment reduced the increased risk to only 20% compared to non-hypertensive patients.

The prevention of acute (non-) fatal vascular events remains a major challenge. Diagnosing PAD in an asymptomatic individual indicates the need of more tight control of hypertension, hypercholesterolemia and hyperglycaemia to obtain optimal secondary prevention. It is thought that asymptomatic individuals with evidence of PAD may well benefit from the same treatments that have proven to be effective in patients with symptomatic atherosclerotic disease.²³ However, the real value of screening asymptomatic individuals for PAD in terms of risk reduction is currently not known. A documented confirmation of the presence of the PAD may assist the initiation of changes in lifestyle of patients, including cessation of smoking, weight reduction, and an increase in physical exercise.

It has been advocated that in individuals with a history of a vascular event, such as PAD, hypertension should be treated more aggressively compared to individuals without a history of a vascular event.²⁴ In individuals with an abnormal ABI, treatment of hypercholesterolemia should be initiated.²⁵ For individuals with diabetes with a significant risk for macrovascular complications, such as diabetics with an abnormal ABI, the target value of HbA1c should be set at the lower limit of 6.5%.²⁶ Also, antiplatelet therapy should be initiated.²⁷

It has been shown that the absolute number of coronary events is greater in the lower risk population than in the high-risk groups.²⁸ In a prospective study, primarily asymptomatic men and women with an average age of 66 years and an abnormal ABI value were shown to have a relative risk of 6.3 for all cardiovascular disease mortality, and 3.1 for all-cause mortality.³ These relative risks are similar to relative risks seen in the secondary prevention setting.³ It has been estimated that simple screening of those individuals aged 50 years or older could potentially prevent around 60 000 major cardiovascular events in Great Britain in the next 5 years. About 85 000 new cases of angina and intermittent claudication may also be prevented, hence about one in 13 treated individuals would acquire some clinical benefit.²⁸

Screening for asymptomatic coronary heart disease or cerebrovascular disease may not be practical, since there are no simple screening tools available at this time. The implication that PAD is strongly associated with coronary heart and cerebrovascular disease makes ABI measurement probably the most efficient screening tool for systemic atherosclerosis. ABI measurement is a simple, inexpensive diagnostic test with an excellent reproducibility among trained operators.²⁹ In addition, it has been shown that assistants in general practice are able to perform ABI measurement correctly.³⁰ This may even lower the costs of screening.

Strengths and weaknesses of the study

First, our study was population-based, was performed in a substantial number of general practices, and included a large number of both men and women.

It is unknown how many potential patients who would have met the inclusion criteria were missed. However, due to the simple inclusion criteria it is assumable that this number of patients was low.

The estimate of the presence of hypertension, hypercholesterolemia and diabetes was based on the established diagnosis of the treating physician. Hence, misclassification of the presence of the risk factors could have occurred, resulting in the underestimation of the role of the particular risk factors in respect of the prevalence of PAD.

In this large, multi-observer study the measurement of ABI was performed by multiple GPs or practice

assistants. This may lead to an observer bias. However, it is reported that this type of bias in regard to the measurement of ABI is as low as 0.114.^{31,32}

Although the described clinical prediction model is based on three well-established vascular risk factors, a validation of this model in the general population would be preferable.

Conclusion

PAD often remains unrecognized because most physicians and patients are unaware of the potential presence, as well as the dangers of this disease. As asymptomatic patients with PAD may well benefit from the same preventive measures that are effective in people with symptomatic disease to prevent a fatal cardio- or cerebrovascular event, screening by ABI in the general population may deliver clinically relevant data. Our PREVALENT clinical prediction model may present the GP with an effective tool to effectively screen the high-risk population in daily practice.

What this paper adds

The recent AHA/ACC guidelines for the management of patients with PAD states that early detection and treatment of PAD, particularly in the populations at risk, may prevent disability and save lives. Measurement of ABI can provide important information about the presence of subclinical atherosclerosis. Performing ABI in the overall population is not feasible due to resource limitations, but it can be used in a selected population. The simple prediction rule could be of use to estimate the risk of an abnormal ABI and screening could be contemplated for a score of seven or higher.

The developed PREVALENT clinical prediction model may present the GP with an effective tool to effectively screen the high-risk population in daily practice.

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Conflict of interest

There was no conflict of interest.

Body giving ethical approval

The study protocol was approved by the medical ethical committee of the Atrium Medical Centre Parkstad, Heerlen, The Netherlands.

Funding body

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Statement of independence

All researchers state their independence from funders.

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