Peripheral arterial occlusive disease : prevalence and diagnostic management in general practice

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Peripheral arterial occlusive disease:
prevalence and diagnostic management
in general practice

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Peripheral arterial occlusive disease: prevalence and diagnostic management in general practice

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Rijksuniversiteit Limburg te Maastricht,
op gezag van de Rector Magnificus,
Prof. Mr. M.J. Cohen,
volgens het besluit van het College van Dekanen,
in het openbaar te verdedigen op
donderdag 1 juni 1995 om 14.00 uur

door

HENRI ELISE JOHANNES HUBERTUS STOFFERS

Promotoren

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Preface

The origin of the Limburg PAOD Study lies with an experienced general practitioner who had become interested in the prevention and treatment of cardiovascular diseases. After a surgeon friend had explained to him the possibilities of the pocket Doppler device for the diagnosis of peripheral arterial occlusive disease (PAOD), he gained experience using this instrument in his own practice. He realised that its use could have important implications for the diagnosis and treatment of patients with PAOD by the general practitioner. It would be easier than before to identify PAOD in patients presenting with leg problems and follow up of treated patients would be more objective. Furthermore, identification of patients with PAOD would imply identification of patients with increased risk for ischemic heart disease and cerebrovascular disease.

This physician worked part-time as a staff member of the Vocational Training programme of the Department of General Practice of the University of Limburg in Maastricht. As the department regularly held conferences on general practice performance, he could discuss his ideas with others. These discussions resulted in a publication on the management of PAOD and in a proposal to the 'Protocol Project' of the cooperating Dutch university departments of general practice.¹ The 'Praeventiefonds', which was asked to finance this project, recommended that a research proposal with respect to PAOD be submitted. With the cooperation of various experts a research project on the natural course and the treatment of PAOD was finally instigated ('Praeventiefonds', 1986).

Given the infrastructure that would have to be developed for this research project, it seemed expedient to develop a complementary study on the diagnostic value of data obtained by history-taking and physical examination in relation to PAOD. Such a project would fit in with the research programme 'Efficacy of diagnostics in general practice' of the Department of General Practice. As a result of the experimental 'General Practitioner Research Training Programme' a proposal for a study on the prevalence and clinical diagnosis of PAOD was formulated.^{2,3} It was awarded a grant from the 'Netherlands Organization for Scientific Research'. This part of the Limburg PAOD Study is the subject of this book. Its official start was January 1988.

Recently, a third study — on the incidence and prognosis of PAOD — has started ('Netherlands Heart Foundation', 1994).

The experienced physician mentioned above was *They Lemmens*, general practitioner in Maastricht from 1959 to 1988 and senior member of the Department of General Practice. He died on 18 September 1990 at the age of 59. He was the spiritual father not only of the 'Limburg PAOD Study' but also of a study on the diagnosis of cardiac arrhythmias ('HRS Study') and a study on the prevention of thromboembolic complications of atrial fibrillation ('PATAF Study').

To me, They also was a mentor in matters concerning personal choices with regard to the triangle 'practice - university - family'. With pleasure I recall his straight forward opinions, our lively discussions, his practical wisdom and — above all — his stimulating enthusiasm. I hope he would have appreciated this first harvest of the scientific tree he helped to plant, the way he used to like the first apples from his orchard.

Henri ('Jelle') Stoffers

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*Streamline flow is silent
Remember that, my boys,
But when the flow is turbulent
There's sure to be a noise.*

*So when your stethoscope picks up
A bruit, murmur, sigh,
Remember that it's turbulence
And you must figure why.*

A.C. Burton

Chapter 1 Introduction

Summary *This book describes studies on the prevalence and diagnostic management of peripheral arterial occlusive disease (PAOD) in general practice. PAOD refers to the manifestation of atherosclerosis in the lower limb distal to the aortic bifurcation.*

There is a number of reasons for paying attention to the management of patients with PAOD in general practice: diagnosis, conservative treatment and monitoring of patients with this chronic disorder are primarily tasks of the general practitioner; the disease may lead to serious complications that should be prevented wherever possible; PAOD is an expression of generalized atherosclerosis; therefore, regular monitoring of risk indicators for cardiovascular disease might be appropriate in PAOD patients.

In this book we try to answer the following principal research questions: 'What is the prevalence of PAOD in a general (practice) population?' and 'What is the diagnostic value of history-taking and physical examination with respect to PAOD?' In addition, we deal with the reproducibility and validity of the ankle-brachial systolic pressure ratio (AB-ratio) in general practice.

Reviews of the literature are presented in the chapters 2 and 3. In chapter 4 the aims of our study are presented. The general methodology of the study is described in the chapters 5 and 6. In the chapters 7 - 10 the results of our studies are presented (reproducibility and validity of the AB-ratio, prevalence of PAOD, diagnostic value of signs and symptoms). In the general discussion our findings are summarized and implications for general practice and future research are discussed (chapter 11).

Basic to general practice is adequate management of somatic problems: superfluous as well as insufficient diagnostic and therapeutic actions should be avoided. The guideline is to start out from a broad set of diagnostic hypotheses which is narrowed down along the way, taking into account not only general practice epidemiology but also the possibility of serious pathology. On the basis of this problem solving process the general practitioner is able to inform the patient about diagnosis and prognosis, to propose therapeutic strategies and to offer advice with regard to supplementary tests or referral to a specialist.¹

Clinical research in general practice

In order to be able to practice this skill, the general practitioner requires descriptive and clinical epidemiological data.^{2,3} Amongst other things, adequate diagnostic management presupposes that the general practitioner knows the prior probability of a disorder — incidence, prevalence — in his patient population or in relevant parts thereof, and knows the diagnostic significance — sensitivity, specificity, predictive values — of diagnostic procedures — history-taking, physical examination,

supplementary tests — applied by him.³

General practice research on the diagnostic value of history and physical examination in specific disorders may contribute to the acquisition of this type of clinical epidemiological knowledge. This is also the case for research on the prevalence of particular disorders — or of the various stages of these disorders — in the general practice population. Research on these clinical aspects of the general practice field is still in its initial phase. Much of the knowledge of the relationships between symptoms and diagnoses derives from medical specialist settings and ought to be reformulated for the general practice 'clinic'.^{3,4}

In contrast to the situation in the (university) hospital, scientific research and health care are physically separated activities in general practice. Health care is provided in the practice, while research is mainly conducted in university departments of general practice. A minority of general practitioners is at home in both worlds. Now and then these worlds meet: when the results of research are presented by researchers to their practising colleagues.

A crucial question is how it may be achieved that ideas for research arising in daily practice are given the opportunity to be transformed into a research proposal. If scientific research in general practice is to remain relevant for general practice care, it is imperative that such opportunities exist. In this respect it is essential that general practitioners have access to a critical but constructive forum and to the scientific literature.⁵

Peripheral arterial occlusive disease: the Limburg PAOD Study

The Limburg PAOD Study is an example of a successful fecundation of 'practice' and 'research'. PAOD — peripheral arterial occlusive disease — is the manifestation of atherosclerosis of the arteries of the lower limb and is the most common peripheral vascular disorder in the elderly. In general practice publications the disease attracts less interest than coronary and cerebral artery disorders. Conceivably, this is because PAOD is generally assumed to run a mild course. Nonetheless, there is a number of reasons for paying attention to the management of patients with PAOD in general practice:

- (early) diagnosis, conservative treatment and monitoring of patients with this chronic disorder are primarily tasks of the general practitioner;
- the disease may lead to serious complications — impaired mobility, severe pain, gangrene, amputation — that should be prevented wherever possible;
- PAOD is an expression of generalized atherosclerosis; therefore, regular monitoring of risk indicators for cardiovascular disease seems appropriate in PAOD patients.

This book presents the report of the first part of the Limburg PAOD Study. We try to answer the following principal research questions:

- What is the prevalence of PAOD in a general (practice) population?
- What is the diagnostic value of history-taking and physical examination with respect to PAOD?

Also the results of research on the reproducibility and validity of the ankle-brachial systolic pressure ratio (AB-ratio) — a noninvasive supplementary test — in general practice are reported.

The general goal of our study is to contribute to a more rational diagnostic approach by the general practitioner of patients with leg complaints in general and PAOD in particular. We also expect to increase the knowledge of the early phase of this disease: after all, it concerns patients with PAOD — including the asymptomatic, atypical and previously unknown patients — as they present themselves to the general practitioner. The results of the studies on the reproducibility and the validity of the 'pocket Doppler method' will add to the discussion on the significance of this device in general practice and in epidemiologic research.

Structure of this book.

In *chapter 2* a survey is presented of the literature on PAOD that was considered relevant for general practice. Considering the main topics of our study attention is focused primarily on data on the prevalence and the diagnostic management of PAOD. *Chapter 3* offers a review of the literature on the measurement of the AB-ratio, which is used as standard diagnostic test in this study.

The literature reviews reveal that a number of gaps exist in the knowledge on PAOD. These gaps are discussed in *chapter 4*, where the main and additional topics of the study are presented. The next chapters describe the methodology of the first part of the Limburg PAOD Study. In *chapter 5* the general design and methods of the study are explained. *Chapter 6* provides a quantitative overview of the selection process and the different populations that can be distinguished in this study.

Then the results of our studies are presented. The *chapters 7 and 8* present the results of our studies on the reproducibility and the validity of the AB-ratio. In *chapter 9* the results of our prevalence study are presented and *chapter 10* offers the results of our analyses of the diagnostic value of clinical signs and symptoms.

The final section of this book starts with a general discussion of the study including its implications for daily practice (*chapter 11*). It ends with a Summary in English and Dutch ('Samenvatting') (*chapters 12 and 13*).

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Chapter 2 Peripheral arterial occlusive disease in general practice. A literature review*

***Summary** This chapter presents a literature review on peripheral arterial occlusive disease (PAOD). The emphasis lies with data regarding the prevalence and the diagnosis of the disease. Literature was gathered systematically from the MEDLINE database and by using the 'snowball method'. This chapter represents the state of affairs known to us in March 1990.*

The reported prevalence of PAOD ranges from 0.2 to 11.7%. It is plausible that many patients will not be known to the general practitioner and that there will be a large category of asymptomatic patients.

The prognosis of intermittent claudication is reported to be relatively favourable: in only about a quarter of patients symptoms progress. However, the prognosis 'quod vitam' of patients with intermittent claudication is rather poor, due to the greatly increased risk of the development of cardiovascular and cerebrovascular complications. Possibly this applies to asymptomatic patients as well.

Little research has been done on the diagnostic significance of signs and symptoms associated with PAOD. From the available data it may be concluded that the current clinical diagnostic methods permit the general practitioner to exclude PAOD, whereas establishing the diagnosis cannot be done with sufficient certainty. Only few data on the diagnostic value of combinations of signs and symptoms are available. In this respect the measurement of the ankle-brachial systolic pressure ratio by means of a pocket Doppler device could be an asset to general practice.

Introduction

In this chapter a review is presented of the literature on PAOD that was considered relevant for general practice. In view of the main topics of this book the discussion is focused in particular to data concerning the prevalence and the diagnosis of PAOD.

* This chapter represents a compilation and revision of the following publications:
Stoffers HEJH, Kaiser V, Lemmens ThGJ, Knottnerus JA. Perifeer arterieel obstructief vaatlijden in de huisartspraktijk: een verborgen ziektebeeld? [Peripheral arterial occlusive vasculopathy in general practice: a hidden disease?] (with English summary). *Huisarts Wet* 1988; 33: 202-6.

Stoffers HEJH, Kaiser V, Zwietering PJ. Perifeer arterieel vaatlijden in de huisartspraktijk. *Bijblijven* 1989; 5: (9)19-26.

Stoffers HEJH, Kaiser V. Wetenschappelijke verantwoording van de NHG-Standaard Perifeer Arterieel Vaatlijden. Utrecht: Nederlands Huisartsen Genootschap, 1990.

Method

From August 1986 the 'Limburg PAOD Study' had a subscription to a two-monthly MEDLINE search via the university library. In the spring of 1988 the automatic subscription was replaced by searches in the MEDLINE database on CD-ROM approximately once per three months. At the time the MEDLINE database comprised articles dating from 1 January 1983. The following keywords were used: atherosclerosis, arteriosclerosis, peripheral arterial occlusive disease, intermittent claudication. The bibliographical entries thus selected were stored in a literature data base on a personal computer. Additionally, the current volumes of general medical journals were kept up with and references were looked up ('snowball method'). Double entries were deleted.

This chapter represents the state of affairs known to us in March 1990.* In order to check on the completeness of the collection of articles requested by us up to that date, our literature database was screened using the following keywords: general practice, family medicine; prevalence, incidence, epidemiology; diagnosis, clinical, signs, symptoms, complaint, subjective, intermittent claudication, findings, peripheral pulse, femoral, dorsal, tibial, trophic, skin, ulcer, examination; doppler, ultrasound; risk factor, predisposition; course, outcome, prognosis.

Prevalence data with regard to PAOD are only relevant to general practice if they stem from studies in moderately selected study populations. Studies using unclear inclusion criteria, an unclear method of patient selection or a highly selected sample of patients — e.g. only men or a narrowly confined age group or a specific risk group — were not considered.

There are three types of studies that produce relevant data on the prevalence of PAOD: morbidity registration studies by general practitioners, population studies on intermittent claudication and population studies using noninvasive tests. However, the results of the various prevalence studies may not simply be compared. A meaningful comparison was made possible by converting age specific prevalence data from these studies to the prevalence of PAOD in a hypothetical general practice of 2350 persons with the age distribution of the Dutch population on 1 January 1989 (i.e. the Dutch standard general practice). Minimal and maximal prevalence figures for each age category were derived from the results of the separate studies in so far as these were available for each category. The figures for all age categories were then combined to yield an estimate of the total prevalence in a standard practice (*table 2.1*). Obviously the validity of these comparisons is limited, given that the data stem from different studies in different populations.

Information on how to take a medical history and perform a vascular physical examination was gathered from general and specific medical textbooks. With regard to the *interpretation of the results of the medical history and vascular examination* two kinds of studies can be distinguished: studies on the variability of the peripheral pulses and studies in which signs and symptoms are compared to the outcome of noninvasive testing. Again, studies in highly selected populations were excluded from this review.

* In Chapter 11 our research findings will be discussed in the light of the most recent literature.

Results

General

The occurrence of atherosclerotic disease is positively influenced by the presence of factors like hypertension, hyperlipidaemia (cholesterol, triglycerides), smoking, diabetes mellitus, obesity, little exercise and stress: the risk factors for cardiovascular disease. For PAOD in particular, risk factors are smoking, the presence of diabetes mellitus or hypertension as well as advanced age and male gender. The literature is not unequivocal as to the significance of raised serum cholesterol and triglyceride levels. In any case cholesterol level appears to be not as important as in ischemic heart disease.¹⁻⁸ All studies indicate that 'smoking' is the most significant risk factor for the development of PAOD and that it is an important parameter for the prognosis of the disease.

Atherosclerosis of the arteries of the limb may lead to a range of ischemic phenomena in the legs: no symptoms (Fontaine stage I), intermittent claudication (Fontaine II), pain at rest (Fontaine III) and (pre-)gangrene (Fontaine IV). The stages III and IV are generally referred to as 'critical ischemia'. These stages are not necessarily successive. In a review by *Dormandy* — discussing mainly outpatient series — was estimated that in three out of four known patients with complaints of claudication symptoms do not progress.⁹ Generally, in approximately 25% of patients presenting with claudication complaints eventually increase. Three to 22% of these patients will undergo vascular surgery — this would correspond to 1-10% of all (known and unknown) subjects with claudication — and 1.5-5% will undergo an amputation.⁹ The probability of clinical deterioration of PAOD or the need for an operation is greater in the first year after the diagnosis than thereafter. Important unfavourable prognostic factors are 'smoking' and 'multiple stenoses'; the level of the vascular occlusion seems less significant.¹⁰⁻¹³

Life expectancy of patients with claudication is approximately ten years less than that of healthy subjects.⁶ Unfavourable factors for the prognosis *quod vitam* are 'smoking', 'multiple stenoses', 'diabetes mellitus' and a 'distal' level of the vascular occlusion.⁹⁻¹⁴ The most important explanation for this reduced life expectancy is the fact that manifest PAOD in its turn is an unfavourable prognostic factor for the development of cardiovascular and cerebrovascular disease.^{7,9} There are indications that for subjects with asymptomatic PAOD the probability of coronary or cerebral arterial disease is increased as well.³ The literature further suggests that patients with PAOD are at increased risk for developing an abdominal aortic aneurysm.^{15,16}

Mortality in patients with PAOD is approximately 2-3 times as high as in subjects of the same age and gender without PAOD. Approximately 75% of the total mortality in patients with PAOD is accounted for by atherosclerosis of the coronary arteries (50%), the cerebral arteries (15%) and the abdominal aorta (10%).⁹ One-fifth of known claudication patients will experience fatal cardiovascular and cerebrovascular complications within five years.¹⁷

Prevalence

In morbidity registration studies by general practitioners, data on PAOD concern patients with symptomatic PAOD — intermittent claudication or advanced stages of PAOD — that are known to the general practitioner.¹⁸⁻²⁰ In general it may be assumed that the diagnosis 'intermittent claudication' will not have been made

Table 2.1 Estimated prevalence figures for PAOD in general practice

Source of the data	Morbidity characteristics	Prevalence*	
		Min	Max
Morbidity registration by general practitioners ¹⁸⁻²⁰	known cases of symptomatic PAOD ($\geq$ Fontaine stage 2), no strict criteria	6	19
Population studies on intermittent claudication ^{6,22-25}	known and unknown cases of symptomatic PAOD - according to 'Rose' ²¹	8	27
	- less strict criteria	45	58
Population study using noninvasive techniques ²³	known and unknown cases of symptomatic and asymptomatic PAOD	approximately 61 - 66	

* n=2350, standardized to the gender and age distribution of the Dutch population on 1 January 1989

strictly according to the criteria of the 'WHO/Rose questionnaire'.²¹ In this group of studies the number of patients known to be afflicted with PAOD ranges from 0.2 to 0.7% of the practice population.

Various surveys on intermittent claudication were performed using oral or written questionnaires, whether or not according to the strict criteria of the 'WHO/Rose questionnaire'. These studies concern patients with intermittent claudication, either known to a medical practitioner or not.^{6,22-25} When strict ('Rose') criteria for the definition of intermittent claudication are maintained prevalence figures range from 1.7% to 4.8%, with most studies reporting percentages just below 2%. The variation in the findings is partly explained by the age distribution of the examined populations.

Population studies carried out by means of noninvasive techniques provide an indication of the prevalence of both symptomatic and asymptomatic PAOD.^{23,26,27} In one study men and women of approximately 40 years and older, selected from the population at large, were examined.²³ The prevalence of PAOD in this sample was 11.7%.

Apparently there is quite a difference between data stemming from different sources. *Table 2.1* presents the estimated number of patients with PAOD in a Dutch standard general practice, recalculated on the basis of the literature. *Table 2.2* presents prevalence figures derived from studies performed in older populations.^{19,23,25} The figures in *table 2.1* suggest that only 10-30% of all PAOD patients would be registered as such in primary health care, that 12-25% of all PAOD patients would be 'asymptomatic' (no intermittent claudication) and that 50-80% of all claudicants would not meet the WHO/Rose-criteria ('atypical' claudication). In the age category 65-75 years (*table 2.2*) general practitioners seem to underregister female patients with intermittent claudication: in population studies the male:female ratio is approximately 1.3, whereas the male:female ratio in the morbidity registration study by *van den Hoogen et al.* is 3.6.

Medical history and physical examination²⁸⁻³⁷

Medical history

The typical symptom of PAOD (stage II) is 'intermittent claudication': the patient

Table 2.2 Prevalence figures for PAOD among elderly subjects by age and gender in three types of studies

Reference	Type of study	Prevalence (%)			
		Gender	65-69 yrs	70-74 yrs	≥ 75 yrs
Hoogen ¹⁹	general practice morbidity registration	male		5.4	9.6
		female		1.5	3.6
		total		3.2	5.9
Evans ²⁵	population study using WHO/Rose-criteria for IC*	male	4.9	5.6	9.6
		female	3.6	4.7	2.8
		total	4.2	5.1	5.5
Criqui ²³	population study using noninvasive methods	male	12	19	23
		female	12	12.5	21.5

* IC: intermittent claudication

complains of pain developing in a leg — usually in the calf — after walking a certain distance. The pain is quickly relieved by rest and reappears when approximately the same distance is covered. The pain arises sooner when walking fast or uphill or when carrying a load. The patient has no complaints while sitting or standing.²¹ PAOD may also manifest itself in a unilateral experience of coldness in the feet. Possibly, the most important criteria for leg complaints due to PAOD are the exercise-related occurrence and the reproducibility of the pattern of complaints: the same complaint of the same severity in the same location after the same exercise.

In stage III the arterial blood flow is insufficient not only during exercise, but also at rest. The patient experiences severe pain, localized especially in the forefoot and in the toes. Initially the complaint occurs only at night when the perfusion pressure is lower due to the horizontal body position and the nocturnal lowering of the systemic pressure (approximately 20 mmHg). Consequently, many patients discover that they may lessen the pain by suspending the leg over the edge of the bed, or by getting up briefly.

A number of differential-diagnostic considerations are represented in *overview 2.1*.

Physical examination

The vascular physical examination consists of inspection of the skin (colour, trophic disorders), palpation of the skin (temperature), palpation of the peripheral pulses and auscultation of the femoral artery. With a normal stethoscope one cannot detect a murmur over the popliteal and pedal arteries.

The classic signs one looks for in a patient suspect for PAOD are: a red-blue skin, a left-right difference in nail growth or hair growth on the (lower) legs or feet, a one-sided cold skin of the lower legs or feet, weak or absent pulsations of the femoral, popliteal, posterior tibial or dorsalis pedis artery, as well as a murmur over the femoral artery. Few authors mention the 'capillary refill' test.^{29,37} Besides these commonly used methods there are a number of procedures that are possibly less common in general practice. By performing the palpation of peripheral pulses and the auscultation of the femoral artery after exercise the sensitivity of these examinations may be increased.^{38,39} By means of the 'dependency-test' according to Rat-schow-Bürger, the 'visual flush method' and the determination of the maximal pain-

Overview 2.1 Differential-diagnostic considerations

Osteoarthritis

- pain at rest (sitting, standing)
- complaints usually worst in the morning
- stiffness with inactivity: pain already on beginning to walk
- after some walking: pain decreases
- after long walking: pain increases
- then standing still: pain decreases only slowly or not at all
- not reproducible: 'good' and 'bad' days
- location: knee, hip, lumbar region

Chronic venous insufficiency

- history of varicosis
- swollen ankles
- tired, heavy, dull, painful sensation in the (lower) legs, also at rest
- nocturnal cramps in the calves
- itch (secondary to dermatitis)
- not reproducible: 'good' and 'bad' days
- more complaints at night than in the morning
- walking: complaints often decrease
- standing: complaints usually increase
- leg elevation: complaints often decrease
- standing occupation

Sciatic pain, lumbar disc prolapse

- backache
- radiation into the leg
- worsened by coughing, sneezing, exerting pressure (LDP)

Peripheral neuropathies

- loss of power, loss of sensation,

paraesthesia, hyperaesthesia

- distal pain
- association with diabetes

Spinal stenosis (pseudoclaudication, Verbiest's syndrome)

- severity of complaints on walking are variable, i.e. not reproducible: 'good' and 'bad' days
- paraesthesia rather than pain
- pain on walking, not on cycling
- standing: pain usually increases
- only when patient sits down the pain decreases
- leaning against wall: pain decreases
- bending back: pain decreases
- carrying heavy object: pain increases

Nocturnal leg cramps

- usually no PAOD
- especially in the elderly
- also occurs in chronic venous insufficiency

Restless legs

- usually no PAOD
- neurovegetative lability?
- iron deficiency?

Especially in young people the following diseases occur

- Thromboangiitis obliterans (Bürger's disease)
- Entrapment of the popliteal artery
- Anterior tibial artery syndrome

less walking distance the functioning of the peripheral circulation may also be tested.^{31,40}

Interpretation of history and physical examination

What is the diagnostic value of a 'typical' pattern of complaints and 'classic' findings on physical examination? Before noninvasive tests were available, already some research has been done on the significance of peripheral pulsations.⁴¹⁻⁴³ These studies showed that an absent dorsalis pedis artery pulse — due to its anatomical variability — often does not indicate PAOD. By contrast, an absent posterior tibial artery pulse does frequently indicate PAOD, and this relationship increases with age. The inter-observer variability in the determination of absent peripheral pulsations is large.⁴²⁻⁴⁴ In one study doctors achieved a fair to good agreement with respect to the palpation of a 'normal' versus an 'absent' pulsation. The agreement

Table 2.3 Signs and symptoms associated with PAOD versus noninvasive testing⁴⁶

Signs and symptoms		Sens. (%)	Spec. (%)	PV+ (%)	PV- (%)
typical claudication		9	99	54	89
skin: erythema, cyanosis, trophic changes, left/right difference in temperature		no research data available			
weak or absent pulsations of the	femoral artery	13	98	47	90
	popliteal artery	no research data available			
	posterior tibial artery	71	91	49	96
	dorsalis pedis artery	50	73	18	93
femoral artery bruit		20	96	37	91
claudication <i>or</i> some disorder of pulse		78	85	40	97
claudication <i>and</i> some disorder of pulse		5	99.6	60	90

PV+: predictive value of a positive test result. PV-: predictive value of a negative test result. 'Some disorder of pulse': diminished or absent femoral, tibial posterior, dorsalis pedis pulse and/or murmur femoral artery. Standard diagnostic method: plethysmography and various ultrasound techniques. Population data: n=575 men and women, aged 38-82 years, prevalence of PAOD = 11.7%.

on the femoral artery pulsations was slightly better than on the popliteal artery pulsations. Regarding the assessment of a 'normal' versus a 'reduced' pulsation, the concordance was not better than by chance, both for the femoral artery and the popliteal artery pulsations.⁴⁴

The introduction of noninvasive tests for assessing PAOD has made it possible to compare complaints and findings of the physical examination to the results of those tests in large study populations.^{26,27,45-47} The noninvasive tests then function as 'gold standard'. Table 2.3 summarizes the results of the only study in a moderately selected population.⁴⁶

No publication on the diagnostic value of the 'capillary refill' test with regard to PAOD was found. In normal subjects the skin should turn from white to red immediately after release of the pressing finger.²⁹ In one study was reported that capillary refill varies with age and gender — upper limit of 'normal' among adult men 2 seconds, adult women 2.9 seconds, elderly 4.5 seconds — and temperature. Given the temperature dependency the authors question the reliability of this sign in prehospital settings.⁴⁸

One publication on the significance of Ratschow-Bürger's test was found, describing a highly selected group of symptomatic patients admitted for surgery. In 'Buerger positive' legs significantly more distal or multiple occlusions on arteriography were found as compared to the 'Buerger negative' group. Also the mean AB-ratio was significantly lower in the 'Buerger positive' group (0.37 vs. 0.62).⁴⁹ Surgeons consider this an important diagnostic test to assess the severity of the disease, i.e. to distinguish between Fontaine stage II and III. An example would be the differentiation between an arterial and a venous origin of the complaint 'pain at rest'. Ratschow's test is less relevant in 'obvious' claudication without signs of

critical ischemia."

Doppler ultrasound

Noninvasive techniques have become increasingly important in the diagnosis of patients with PAOD. Since the 1970s special 'vascular laboratories' were set up in many clinics.⁵⁰⁻⁵⁶ One of the techniques based on the application of ultrasound is the measurement of the ankle-brachial systolic pressure ratio (AB-ratio). The principle of this technique is simple: a vascular stenosis causes a fall in blood pressure distal to the stenosis. By means of a 'Doppler stethoscope' — a convenient instrument that transmits ultrasound and receives the sound waves reflected by moving erythrocytes — and a sphygmomanometer the systolic blood pressure can be assessed accurately: the blood pressure thus measured agrees closely with the pressure registered intra-arterially.^{27,57-60} By measuring the blood pressure both proximal and distal to the expected stenosis one may determine whether a fall in pressure, i.e. a stenosis, is present in the course of an artery.

Accordingly, the systolic pressure at the arm (brachial artery) and the ankle (posterior tibial or dorsalis pedis artery) are measured to determine whether there is a stenosis in the arterial circulation of the lower limb. The relationship between the arm and ankle pressures is expressed as the 'ankle-brachial systolic pressure ratio'.⁴⁴ It is represented as a fraction or a percentage. In contrast to the angiogram, the AB-ratio is not an anatomical but a functional measure of the arterial circulation in the lower limbs. The method is unreliable in patients with incompressible blood vessels due to mediasclerosis, a condition that may be found in diabetic patients. In these cases erroneously high systolic blood pressures are measured.

In healthy persons the average AB-ratio lies between 1.00 and 1.20. *Table 2.4* shows how the values of the AB-ratio may be interpreted according to the literature.^{50,53,61-65} From this table one may deduce that it is not possible to distinguish sharply between 'no', 'mild' and 'major' vasculopathy. In general an AB-ratio >1.00 indicates that there is no PAOD, while an AB-ratio <0.90 renders PAOD very probable.

The ankle pressure is related to the prognosis of an individual patient: an ankle pressure exceeding 70 mmHg means that the probability of an operation or an amputation in the future is minimal.^{10,11} The course of PAOD may be observed by means of AB-ratios determined at intervals. The difference between two successive AB-ratio measurements should be at least 0.10-0.15 in order to be able to speak of a clinically relevant improvement or deterioration.^{11,66,67}

In cases with an uncertain diagnosis the AB-ratio may be measured after exercise: in a patient with PAOD the initially normal AB-ratio decreases to an abnormal value. Thus, the number of false negatives will be reduced. In the vascular laboratory often a treadmill is used, whether or not tilted at a specific angle and running at a particular speed (e.g. 4 km/h). The patient walks for a fixed period (e.g. 5 minutes) or until the pain forces him to stop.⁶⁵

An alternative is the post-occlusion reactive hyperaemia test.⁶⁸⁻⁷¹ The AB-ratio

* PJEHM Kitslaar, JA Lawson, personal communications to the working party on 'Peripheral Arterial Disease' of the Dutch College of General Practitioners, spring 1990.

** or: ankle-arm-index, ankle-arm-ratio, ankle-brachial index, ankle-brachial pressure index, AB(P)I, Winsor index etc.

Table 2.4 Interpretation of the values of the AB-ratio^{50,53,61-65}

Value AB-ratio	Clinical picture. Angiographic conclusion
> 1.00	Generally no complaints. No severe stenosis or occlusion.
< 0.90	Usually there are complaints. A rather severe stenosis is almost always present.
0.50-0.90	Intermittent claudication is usually present (Fontaine II). A rather serious stenosis or a single occlusion is usually present.
< 0.50	Generally there is pain at rest and/or pain at night and/or trophic disorders (Fontaine III). Multiple occlusions may be present.

is measured repeatedly during the hyperaemic period that follows the quick release of the sphygmomanometer cuff, which has been placed above the ankle with supra-systolic pressure for 3-5 minutes. This method, which in theory could also be carried out in general practice, is sufficiently reproducible. In addition, the reactive hyperaemia test may be carried out not only in the absence of ECG control but also for both legs separately, which is not the case for the treadmill test. However, this theoretically ideal method requires 30-45 minutes per patient and can be painful. The reproducibility of the test is reported to be inferior to that of the resting AB-ratio measurement. These properties make the reactive hyperaemia test less feasible to the general practitioner.

An exercise test available to the general practitioner is having the supine patient perform plantar flexion/extension (calf exercise) or flexion/extension of the knee (exercise of the upper leg) during two minutes in which the general practitioner's hand serves as a springy resistance.^{50,72}

Therapy

Despite the uncertainties that still exist with regard to the course and the prognosis of PAOD, it appears possible to halt the progression of the disease. For the general practitioner, conservative therapy is of particular importance.^{73,74} The rationale of advice to be given by the general practitioner is to influence risk factor status. Daily walking exercises and the cessation of smoking have proved to be effective.⁷⁵⁻⁹³ Maintaining a low-fat diet has a positive influence on the course of the atherosclerotic process in general, but its effect on the amelioration of PAOD is small.⁹⁴⁻⁹⁷ Proper foot-care is also important, especially in PAOD patients with diabetes.

Drug therapy in PAOD is still controversial.^{73,98-101} There are no rational arguments that support the use of vasodilator drugs: post-stenotic vascular dilatation is already maximal in PAOD. Furthermore, vasodilators possibly induce a 'steal' effect in non-diseased vascular areas.^{102,103} Anticoagulant therapy has been used in the past to prevent complications of PAOD. However, the effectiveness has proved to be small and probably does not balance the potential side-effects.^{100,104} Research on the effect of treatment of symptomatic patients with platelet aggregation inhibitors such as salicylic acid derivatives is ongoing.¹⁰⁵⁻¹¹⁰ The 'rheological drugs' pentoxifylline and buflomedil have been proven effective in improving the walking distance of patients with severe PAOD.¹¹¹⁻¹¹⁵ They might be prescribed when other therapeutic interventions are inappropriate or have failed.

Concerning the developments in vascular surgery we must be brief here. An important development of the last years is that the indication for arteriography and vascular surgery has become more strict, owing to the development of noninvasive diagnostic procedures.^{51,52,54,56,64,65,116,117} Besides this, the improvement in vascular reconstructive techniques and the increasing experience with percutaneous transluminal angioplasty need to be mentioned.^{118,119}

Discussion

General

From the literature it appears that much is still unclear about the natural course and the prognosis of PAOD. It is certain that patients diagnosed as having 'PAOD' bear a high vascular risk. PAOD, ischemic heart disease and cerebrovascular disease must be seen — not only theoretically but also actually — as manifestations of a single disorder: atherosclerosis. A patient with PAOD therefore deserves a full vascular physical examination. As far as risk factors are concerned, the general practitioner at least could pay attention to the important role played by smoking in the development and progression of PAOD and the beneficial effect of cessation of smoking on the course of the disease.

Prevalence

The data presented in the *tables 2.1 and 2.2* suggest that many PAOD patients are not known to the general practitioner. A British population study in which the patients of two general practices were asked to participate, disclosed that only half of all persons with complaints of claudication had consulted a doctor.⁶ Similarly, in his review *Dormandy* concluded that probably at least half of all patients with intermittent claudication are unknown.⁹

It is not clear how many patients with claudication actually exhibit a 'typical' picture ('Rose') and how many report a less distinct or different pattern of complaints. The data of *tables 2.1 and 2.2* give reason to assume that there is a large group of 'asymptomatic' and 'atypical' PAOD patients. In studies where a history is taken by means of the WHO/Rose questionnaire these types of patients are missed by definition. Furthermore, it turns out — provided that figures from studies using noninvasive tests may indeed be extrapolated to general practice — that the number of patients with PAOD in a Dutch 'standard general practice' would amount to 61-66.

Medical history and physical examination

Regarding the interpretation of diagnostic data derived from the history and the physical examination (*table 2.3*) the general conclusion can be that the predictive values of negative (normal) findings were found to be high and the predictive values of positive (abnormal) findings were found to be low. The high predictive values of negative findings imply that it would be well feasible to exclude PAOD on the basis of standard clinical-diagnostic methods. The low predictive values of positive findings imply that PAOD can be ruled in with less certainty. A rule of thumb could be 'the more positive findings, the more probable the diagnosis PAOD'. There are no data to quantify this statement.

If a 'typical' history ('WHO/Rose questionnaire') is taken, then the asymptomatic

and atypical patients are missed by definition. Possibly, the sensitivity of the history will be improved by inquiring after less typical symptoms or sensations, whereas the specificity might be increased by asking additional differential diagnostic questions (for example, about the effect of walking, standing, sitting and cycling, about the occurrence of 'good' and 'bad' days, and about the presence of paraesthesias, loss of power or loss of sensation).

Doppler ultrasound

An important question is to what extent the general practitioner is able to diagnose PAOD — at an early stage — in his practice population if he thinks in terms of a 'typical' pattern of complaints (i.e. intermittent claudication) and of 'classic' findings on physical examination (i.e. decreased peripheral pulsations, a murmur in the groin and trophic disorders). The measurement of the AB-ratio by means of the Doppler ultrasound method appears to be a potentially useful supplement to the clinical diagnostics currently used by the general practitioner. In *chapter 3* the literature on the Doppler method will be reviewed more closely.

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Chapter 3 Noninvasive vascular tests in general practice. A literature review.*

Summary *The measurement of the resting ankle-brachial systolic pressure ratio (AB-ratio) by means of a pocket Doppler device is a noninvasive technique used for diagnosing peripheral arterial occlusive disease (PAOD). In the present chapter the literature on the reproducibility and the validity of this method is examined. In addition the merits of the pocket Doppler device are compared to the possibilities of a vascular laboratory. Literature was gathered systematically from the MEDLINE database and by using the 'snowball method'. This chapter represents the state of affairs known to us in March 1990.*

The reproducibility of the AB-ratio measurement is reported to be acceptable: the 95% prediction interval around a measured value is ± 0.14 to ± 0.20 .

Using the resting AB-ratio it appears well feasible to differentiate between angiographically 'non-diseased' and 'occluded' arteries. The distinction between 'non-diseased' and 'stenosed' vessels seems less clear.

The selection of a cutoff value for the AB-ratio in the 0.90 to 1.00 range is open to discussion. In the most valid studies sensitivity varies between 75 and 97% and specificity between 92 and 100% at a cutoff point of 0.90. Pooling the results of four comparable studies yields 82% for mean sensitivity and 98% for mean specificity.

The vascular laboratory is able to offer diagnostic information that is harder and more comprehensive than the pocket Doppler measurements. However, applying the pocket Doppler device in general practice may lead to a more selective management with regard to treatment and referral.

Introduction

In chapter 2 we suggested that the measurement of the resting AB-ratio by means of a Doppler device could play a useful role in general practice. The general practitioner might use the measurement of the AB-ratio as an aid in diagnosing PAOD and in estimating the prognosis, as a method for following up the course of the disease or the effect of treatment, and for improved documentation of a referral to the vascular specialist. The principle of the measurement of the AB-ratio was also discussed in the former chapter.

In this chapter the following questions are dealt with:

* An abridged version of this literature study was published as part of: Stoffers HEJH, Kaiser V. Wetenschappelijke verantwoording van de NHG-Standaard Perifeer Arterieel Vaatliden. Utrecht: Nederlands Huisartsen Genootschap, 1990.

- 1 Is the measurement of the resting AB-ratio sufficiently reproducible?
 - 2 Is the measurement of the resting AB-ratio a valid method for making the diagnostic decision 'PAOD: present/absent'?
 - 3 What position does the simple hand held Doppler device take in comparison to the vascular laboratory:
 - a are there relevant differences in the measurement of the resting AB-ratio in the vascular laboratory as compared to general practice?
 - b what are the supplementary possibilities offered by the vascular laboratory?
- The answers are important with respect to the evaluation of the relevance of the resting AB-ratio measurement for general practice and for epidemiological research on PAOD.

Methods

In connection with the first two questions literature on PAOD and noninvasive vascular tests was gathered according to the procedure described in *chapter 2* (MEDLINE, snowball method, literature database on personal computer). Relevant titles were searched for in March 1990 by means of the following keywords: epidemiology, diagnosis, Doppler, ultrasound, validity, accuracy, precision, reproducibility. Each of the articles thereby collected was assessed on its quality and relevance.

The interpretation of the literature on the **reproducibility** of the measurement of the resting AB-ratio is hampered by several factors: the method used to determine the 'reproducibility' was usually described insufficiently; the parameters used to represent the 'reproducibility' were not uniform and could not simply be compared; generally, the observers were experienced staff members of surgical departments or vascular laboratories rather than general practitioners or practice assistants. One way to compare the results of different studies, is to calculate the '95% prediction interval' around the measured value of the AB-ratio, on the basis of the standard deviations of the various components of variability given in (or deduced from) the articles concerned.*

The assessment of the **validity** of the measurement of the AB-ratio for general practice with respect to the distinction 'PAOD: present/absent' on the basis of literature, is also encumbered by several factors. All studies were carried out in surgical or medical (outpatient) departments rather than in a primary health care setting. In the specialist's office there will be few or no patients in an early phase of PAOD. In general, tests were performed on persons with complaints. For 'controls' either healthy volunteers — i.e. subjects without complaints — or the 'healthy legs' of patients with PAOD were used. When the control group consisted of volunteers angiography was usually not performed on these subjects, whereas in patients it was. By contrast, when the control group comprised 'healthy legs' of patients with PAOD, an angiogram was made. Only rarely was discussed whether Doppler testing and clinical examination or angiogram were performed independently. Usually the noninvasive tests were performed before angiography. It was not always clear whether the data were analysed prospectively or retrospectively. Those studies in which the conclusion 'normal' was based on an angiogram may be considered

* Formula: 95% prediction interval = $1.96 * \sqrt{(\sum SD^2)}$

the most valuable.

With respect to question 3, in addition to the literature study a **vascular laboratory** was visited. It was observed how several measurements were performed.*

Results

Reproducibility

Eleven studies contained data on the variability of the measurement of the AB-ratio.¹⁻¹¹ The results from the four best studies (criteria: adequate description of patients, observers, method and design of analysis) were used to estimate the 95% prediction interval of the AB-ratio. This interval comprises the range of AB-ratio's between the measured value $\pm$ (0.14 to 0.20).^{3,4,8,9} It concerns the total variability (i.e. the sum of measurement and biological variability). In general, the stage of the disease — i.e. the mean value of the AB-ratio — does not seem to influence the reproducibility. The difference between two measurements of the AB-ratio on different occasions in order to assess the course of PAOD, is only statistically significant and clinically relevant when it is greater than 0.15.^{7,8,11}

Validity

Fifteen studies containing data on the diagnostic validity of the AB-ratio were found.^{1-3,6,12-22} *Table 3.1* provides an overview of the sensitivity and specificity reported in six studies in which the conclusion 'normal' was based on angiography and thus may be considered the most useful.^{3,13-17} Pooling the results of four studies using comparable criteria for 'diseased/healthy' yields a weighted mean sensitivity of 82% (230/282) and a weighted mean specificity of 98% (88/90) if 0.90 is used as cutoff point for the AB-ratio.^{13-15,17} Using a cutoff value for the AB-ratio of 1.0 these figures would be 88% (115/130) and 81% (30/37) respectively.¹³⁻¹⁵

In some studies a different method was used to assess to what extent one may differentiate between 'healthy' and 'diseased' legs by means of the AB-ratio.^{13,18,19} In these studies the distribution of the AB-ratio in a population of angiographically normal vessels is compared to the distribution of the AB-ratio in a population of vessels with angiographic abnormalities. It then turns out that 'healthy arteries' and 'occluded arteries' can be readily distinguished. The distinction between 'healthy vessels' and 'stenosed vessels' can possibly not be made as clearly.

Comparing the Doppler result to the clinical picture indicates that the group of patients without complaints overlaps the group of patients with intermittent claudication. The overlap in the AB-ratio especially concerns patients with 'moderate' complaints of claudication.²⁰⁻²²

Comparison with the vascular laboratory

The literature usually deals with the measurement of the AB-ratio as it takes place in vascular laboratories. Compared to the pocket Doppler measurement there are both similarities and differences (*table 3.2*). The most important skill — fixing the transducer at a correct angle and under adequate pressure — is similar in both situ-

* details mentioned are as in use in the Vascular Function Department of the University Hospital Maastricht

Table 3.1 Sensitivity and specificity of the measurement of the resting AB-ratio^{a,b}

Reference	Cutoff value	Sensitivity	Specificity
Buth ^{3 c}	0.85	247/249 = 99%	50/50 = 100%
Thulesius ^{13 d}	0.88	64/66 = 97%	40/40 = 100%
Chamberlain ¹⁴	1.00	49/55 = 89%	4/5 = 80%
	0.90	43/55 = 78%	4/5 = 80%
Hylkema ¹⁵	1.00	66/75 = 88%	26/32 = 81%
	0.90	56/75 = 75%	32/32 = 100%
Hylkema ^{16 e}	1.00	132/132 = 100%	32/53 = 60%
	0.90	132/132 = 100%	49/53 = 92%
Smith ¹⁷	0.90	67/86 = 78%	12/13 = 92%

^a the figures presented below derive from 2x2 tables that were *deduced* by the authors of this chapter from the results reported in the reference concerned

^b criterium for normal and abnormal (stenoses and occlusions) based on angiography

^c in contrast to the other studies, the figures here refer to the worst legs of the subjects only, and the study was carried out retrospectively.

^d in subjects less than 40 years old, no angiography was performed in subjects without any clinical signs of PAOD

^e not included in the analysis were subjects with angiographic abnormalities but without complaints and subjects with complaints but without angiographic abnormalities

ations. It is to be expected that the greater and continuous experience of the vascular laboratory technicians contributes to a better reproducibility of the vascular laboratory measurement. The differences in measuring instruments may lead to a somewhat better fixation of the Doppler device in the vascular laboratory — particularly in the measurement of the ankle pressure — and to obtaining slightly higher pressures in the vascular laboratory. All these differences may, in theory, lead to somewhat higher AB-ratios in the vascular laboratory as compared to general practice.

The vascular laboratory offers a number of diagnostic possibilities that are too laborious or too expensive for routine use in general practice:^{3,15,18,24-32}

- the determination of the post-exercise AB-ratio can reveal cases of PAOD who have a normal resting AB-ratio; it provides information on the cardiopulmonary and locomotive functioning of the patient;
- the post-occlusion reactive hyperaemia serves the same goal, but can be used with patients for whom cardiopulmonary exercise is not appropriate;
- the systolic toe pressure can be measured in cases where the AB-ratio is not accurate, e.g. in patients with mediasclerosis;
- by using the Doppler device at different levels of the leg, segmental blood pressure measurements can be taken, enabling diagnosis of the location of a stenosis;
- by analysing the pulse waves (visual spectrum analyzed Doppler signal) at distinct levels, the stenosis can better be located and the degree of dysfunctioning of the vessel assessed;
- these tests may, if necessary, be supplemented with the so-called 'duplex scan',

Table 3.2 Comparison of the measurement of the AB-ratio in general practice and in a vascular laboratory*

	General Practice	Vascular Laboratory
Observers:	general practitioners, practice assistants	VL technicians
- experience	variable; not daily	every day again
Procedure:		
- transducer	8 MHz, pen-shaped R hand fixes (angle, pressure) manual inflation by bulb (L hand)	8 MHz, pen-shaped R hand fixes (angle, pressure) automatically by pressing 1 button (L hand)
- inflation of cuff	manual deflation using valve (L hand)	automatically by pressing 1 button (L hand); rate set in advance
- deflation of cuff	adjustable small speaker, sensitive to background noise	adjustable large speaker, hardly sensitive to background noise
- sound	Hg-column with mm scale or dial with hand and mm scale	large dial with hand and mm scale
- taking of reading	flexion/extension (not standardized)	walking test (treadmill running at a speed of 4 km/h; the patient walks for 5 minutes or until the pain forces him to stop)
- stress test		

* based on observations of the procedure in the Vascular Function Department of the University Hospital Maastricht

which is a combination of B-mode ultrasound ('picture') and Doppler pulse wave analysis ('flow'), permitting examination of individual blood vessels.

The goal of the latter three techniques is to locate stenoses and to assess their hemodynamic consequences.

Discussion

Reproducibility

The reproducibility of the AB-ratio measurement may be considered acceptable: the 95% prediction interval around the measured value varies between $\pm (0.14 - 0.20)$. This relates to the sum of measurement variability and biological variability. It is important that the inexperienced assessor schedules sufficient time to allow for re-measurements, in order to attain an outcome of which he feels certain. The long-term biological variability constitutes a reason for repeating the measurement within a few weeks.

Validity

In investigating the validity of the determination of the AB-ratio, the methodological remarks that can be made (study population, spectrum of the disease, gold standard, independence) imply that data concerning the high sensitivity of the measurement of the AB-ratio are better supported than statements about the high

specificity. Nonetheless, the literature permits the conclusion that the measurement of the resting AB-ratio is a valid method for distinguishing between 'healthy' and 'occluded' vessels. It appears that the distinction between 'healthy' and 'stenosed' vessels can be made less clearly. Thus, the measurement of the resting AB-ratio seems less valuable for the detection of minor (angiographic) vascular abnormalities.

As a consequence of this fact the choice of the cutoff point for the AB-ratio is open to discussion. There is a grey zone between 0.90 (higher specificity) and 1.00 (higher sensitivity). For general practice it would seem that 0.90 is to be preferred, the specificity becoming too low otherwise: with a relatively low prevalence (see *chapter 2*) a high specificity is essential in order to obtain an acceptable predictive value of a positive test result. On the other hand, sensitivity should not be too low: from a preventive perspective it is important to find cases with relatively mild PAOD. The higher number of false positive test results in case of a higher cutoff value, could be diminished by repeating the measurement a few times on consecutive occasions. For other medical disciplines or for epidemiological research other considerations may hold.

Comparison with the vascular laboratory

The most important manual skill required for assessing the resting AB-ratio in general practice is more or less identical to that in the vascular laboratory. However, the theoretical comparison of the measuring procedures leads one to expect that the reproducibility in general practice is lower.

It also may be presumed that the values for the AB-ratio obtained in general practice are systematically somewhat lower than the values measured in the vascular laboratory. This means that some of the subjects whose AB-ratio is close to the cutoff point would be labelled as 'PAOD' in general practice but not in the vascular laboratory. Thus, in addition to the reproducibility argument mentioned above, there is a second reason to repeat the measurement of the AB-ratio within a few weeks: reduction of the number of false positive cases.

The vascular laboratory offers supplementary possibilities. If clinical picture and resting AB-ratio do not produce enough evidence to establish the diagnosis, a treadmill test, reactive hyperaemia test or the measurement of the systolic toe pressure can yield additional information. Pulse wave analysis, measurement of segmental pressures and performing a duplex scan can provide information on the anatomical location and hemodynamic consequences of arterial stenoses.

Conclusions

The AB-ratio at rest differentiates between obvious and no PAOD. When an AB-ratio < 0.90 is (repeatedly) found, this could be an argument for giving the patient specific advice with regard to smoking and exercise. The AB-ratio offers an impression of the severity of the disorder. Moreover, the ankle pressure provides an indication for the prognosis. The AB-ratio also permits monitoring the course of the disease and a better documentation of any referrals to the vascular specialist. A decrease in the AB-ratio exceeding 0.15-0.20 could be a reason for referral with a therapeutic goal.

The pocket Doppler device may be useful in general practice. It may reduce the number of referrals, namely those cases that would primarily be referred for dia-

Table 3.3 Proposal for the interpretation of the resting AB-ratio in general practice, taking criteria for reproducibility and accuracy into account, as discussed in this review

AB-ratio (pocket-Doppler)	Interpretation (in general practice)
> 1.05	PAOD may be ruled out confidently
0.90-1.05	PAOD cannot be ruled out, but a repeatedly measured value of more than 0.90 renders the presence of the disease unlikely*
0.75-0.90	A healthy vascular system cannot be ruled out with certainty, but a repeatedly measured value of less than 0.90 renders the presence of PAOD (stenosis, single occlusion) very probable
< 0.75	PAOD (stenosis, occlusion) is definitely present
< 0.50	Multiple occlusions are probable

* a normal resting pressure followed by an abnormal post-exercise AB-ratio indicates PAOD

gnostic purposes and not for surgical intervention. On the basis of the literature discussed, guidelines for the indications, the execution, and the interpretation (*table 3.3*) of noninvasive tests in general practice may be drawn up in a pragmatic fashion.³³

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Chapter 4 Aims of the empirical studies

Summary *The main objectives of this study are to answer the following questions:*

1 *What is the prevalence of peripheral arterial occlusive disease (PAOD) in the general practice population?*

2 *What is the diagnostic significance of signs and symptoms in PAOD?*

In addition we want to study the following issues:

- *The reproducibility of the measurement of the ankle-brachial systolic pressure ratio.*
- *The diagnostic power of the measurement of the ankle-brachial systolic pressure ratio.*

In the literature review of *chapter 2* it is rendered plausible that PAOD occurs more frequently than is generally thought: there are many patients with PAOD of whom the general practitioner is not aware, both with and without complaints. In addition there seems to be an underregistration of female patients with intermittent claudication.

Much is still unclear about the natural course and the prognosis of PAOD but it is certain that patients diagnosed 'PAOD' are at high cardiovascular risk. Early diagnosis leading to timely conservative intervention might possibly procure a decrease in the progression of the atherosclerotic process and a reduction of the cardiovascular and cerebrovascular morbidity and mortality. In this respect the clinical relevance of 'asymptomatic' PAOD is still unclear.

There is a paucity of scientific information concerning the predictive values of data obtained from the medical history and the physical examination with respect to PAOD in general practice. Possibly, the classic textbook pattern should be modified for the general practice setting. The diagnostic value of combinations of signs and symptoms is unknown.

A number of questions therefore remain. For instance: can the value of the history (read: Rose questionnaire) be improved by elaborating it with questions relating to 'less typical' complaints, differential diagnostic questions and questions about risk factors? What is the value of signs and symptoms other than those discussed in the literature? Would it be possible to identify combinations of procedures that provide optimal information about the probability of the diagnosis 'PAOD'? Do atypical complaints occur more often in women than in men? Would it be possible to discern a characteristic pattern of signs and symptoms for the early phase of the disease in patients with manifest PAOD as well as in subjects initially considered asymptomatic?

In *chapter 3* we concluded that the measurement of the AB-ratio using a hand held Doppler device could be a useful supplementary test in general practice. However, there is reason for some reserve regarding the introduction of this diagnostic method in general practice. Validity and reproducibility have not been examined in

populations relevant to general practice, using methods that are feasible in this setting. Factors such as the spectrum of the disease, the nature of decision-making in general practice and the use of the Doppler device by general practitioners or practice assistants — in stead of vascular laboratory technicians — may influence the validity and the reproducibility of the measurement of the AB-ratio considerably.

Accordingly, empirical research on the validity and the reproducibility of Doppler testing in general practice remains necessary. Research on the reproducibility of the AB-ratio in general practice should be carried out with patients from general practice and with general practitioners or their assistants as observers. Research on the validity of the method should take the spectrum of signs and symptoms occurring in general practice into account. In addition it should be relevant to the diagnostic situation of the general practitioner. Then, predictive values of positive and negative Doppler test results could be assessed.

The outcomes of this type of research are important for deriving a judgment on the value of the pocket Doppler for general practice and for epidemiological research on PAOD in relatively unselected populations.

Thus, in view of the gaps in knowledge identified by analysis of the literature and of our possibilities for research in general practice, the following **principal research topics** were formulated:

- 1 What is the prevalence of PAOD in the general practice population, and how large are the categories 'asymptomatic', 'atypical' and 'manifest' PAOD, known and unknown to the general practitioner?
- 2 What is the value of clinical data (history, physical examination, patient record) for the diagnosis of PAOD? Or: What are the sensitivity, the specificity and the predictive values of clinical data — both separately and combined — in relation to PAOD?

Since we intended to use the ankle-brachial systolic pressure ratio (AB-ratio) by means of a hand held Doppler device as 'standard' diagnostic test, the following **additional research topics** were formulated:

- Regarding the reproducibility of the measurement of the AB-ratio:
 - What is the magnitude of measurement variation due to the multi-observer design of the Limburg PAOD Study?
 - What is the magnitude of other sources of measurement variation, relevant to clinical situations?
- Regarding the diagnostic power of the measurement of the AB-ratio in general practice:
 - What is its accuracy and diagnostic value?
 - What is its optimum cutoff value?
 - Can we provide threshold cutoff values beyond which PAOD can be ruled in (high predictive value of a positive test result) or out (high predictive value of a negative test result)?

Chapter 5 Design, methods and variables*

Summary This chapter discusses the general design, methods and variables of the main study on the prevalence and clinical diagnosis of peripheral arterial occlusive disease (PAOD). The definitive study population was recruited from a population of male and female patients — born between 1 November 1911 and 31 December 1946, on the list of 18 general practice centres — by means of a postal questionnaire on complaints and risk factors (yielding a 'prior risk score' ranging from zero to five) followed by a sampling and selection procedure.

Data collection in the general practice centres occurred according to a cross-sectional design and consisted of two parts which had to be executed independently:

- 1 data from the medical history were provided by the patient in a questionnaire and data on findings of the physical examination, previous medical history, medication, co-morbidity and diagnosis were collected by the general practitioner.
- 2 the measurement of the ankle-brachial systolic pressure ratio (AB-ratio) by means of a pocket Doppler device was carried out by a practice assistant. This 'Doppler measurement' was used as standard diagnostic test. Patients with an AB-ratio lower than 0.95 on two consecutive occasions (interval: one week) were considered to have PAOD.

All the anonymous and coded variables described in this chapter were read into the university's mainframe computer. Personal details of the patients were stored separately in a database on a personal computer.

Methodology and results of the additional studies on the reproducibility and the diagnostic validity of the measurement of the AB-ratio will be discussed in chapters 7 and 8.

Introduction

Mid 1986 the Department of General Practice started a research project on the natural course of peripheral arterial occlusive disease (PAOD) and the effect of calcium-carbasalate on that course (the Limburg PAOD Study). The longitudinal data collection of this project (a combination of a cohort study and a randomized controlled trial) would be preceded by a phase during which patients with PAOD would have to be identified.

While preparing this study, the idea arose to expand the case-finding phase to a

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cross-sectional study on the prevalence and diagnosis of PAOD in general practice. It would cost relatively little extra effort to gather data on these topics. The measurement of the ankle-brachial systolic pressure ratio (AB-ratio) using a pocket Doppler device, which was used as a screening instrument in the longitudinal study, could be employed as standard diagnostic test.

In this chapter an overview is presented of the design of the cross-sectional study, the 'prevalence & diagnosis' study (Limburg PAOD Study, part 1) as it was embedded in the 'course & intervention' study (Limburg PAOD Study, part 2).

Populations and selection procedure.

Original design of the selection procedure

In the first instance, the size of the study was determined by the requirements of the 'course & intervention' study. Both studies were to be carried out in 20 general practices, with a total population of approximately 60 thousand subjects. It was expected that in the age category '40 to 75 years' (the 'source population': approximately 30 thousand subjects) a postal questionnaire would identify 5-6000 patients at risk for PAOD. These subjects, plus a sample of 1000 persons not at risk according to the answers provided in the postal questionnaire, would be asked to take part in the study. The group of patients which would subsequently be examined in the general practice centres (the 'study population') was to yield the subjects with PAOD suitable for participation in the longitudinal study (the 'follow-up population'). The original design of the 'prevalence & diagnosis' study is presented in *figure 5.1*.

The lower age limit was chosen arbitrarily because PAOD is a realistic possibility mainly in people of 40 years and older. The upper age limit was chosen arbitrarily on account of requirements posed by the 'course & intervention' study: a greater drop-out percentage was expected with increasing age (co-morbidity, mortality, protracted hospital admissions), as well as decreased mobility, low compliance (cessation of smoking, daily exercise, daily drug intake), and a diminished relevance of the (long-term) intervention.

General practice centres and patients

The cooperation of the participating general practitioners (and their practice assistants) was obtained by means of a short course on PAOD, an informative session concerning the study, and personal contacts. Altogether, 32 general practitioners of 20 general practices with 23 practice assistants agreed to take part. The collaboration was laid down in a contract. The services offered would be remunerated. Moreover, all practices were supplied with a pocket Doppler device.

For this clinical and epidemiologic study, compliance with the research protocol and good motivation of the general practitioners were regarded more important than the regional or national 'representativeness' of the general practitioners. The recruitment methods were not expected to lead to relevant selection bias in relation to PAOD in the general population.

The personal details of all patients born between 1 January 1911 and 31 December 1946 were obtained from the administration of the participating general practitioners (mostly through manual work by the practice assistants, partly supplied on diskettes) and from the regional sick fund (diskette). All personal details were stored

Figure 5.1 Original design of the Limburg PAOD Study

in a database in the personal computer of the project. Altogether, personal details of 30051 persons were obtained.

The postal questionnaire

In order to increase the efficiency of the identification of PAOD cases in the population to be selected for further study, all patients of whom personal details had been acquired were sent a questionnaire consisting of seven yes/no questions on complaints (pain while walking, cold feet) and risk factors for PAOD (smoking more than 15 cigarettes a day, hypertension, diabetes mellitus, a medical history of cardiovascular disease or a family history of cardiovascular disease) (*appendix 5.2*). The patients were asked to complete and return the questionnaire. The non-response was kept to a minimum by enclosing information on the study, by using note-paper of the patient's general practice, by requesting that the general practitioner would co-sign the covering letter, and by providing a post-paid envelope. Non-responders were sent up to two letters of reminder.

The aim was that all patients who had answered at least one question affirmatively (prior risk score ranging from 1/7 to 7/7) would be invited for an examination by their general practitioner. In addition, a sample would be taken from the category of subjects without increased risk (prior risk score = 0/7). This sample would yield information on the prevalence of PAOD in the most healthy subpopulation. This was also necessary in order to be able to compute the total prevalence in the source population by calculating back from the prevalence measured in the sampled fraction.

Adjustment of the selection procedure

When the first results of the postal questionnaire came in, it turned out that the number of people with a prior risk score $\geq 1/7$ was much larger than expected. This was partly attributable to the question concerning a family history of cardiovascular disease. Had the initial criterion for participation in the study (prior risk score $\geq 1/7$) been maintained, then 15-16000 people would have had to be examined by their general practitioner. This being infeasible, the selection procedure was adapted.

The population to be examined by the general practitioner had to meet all of the following conditions:

- the prevalence estimation had to be possible;
- it had to be possible to compare the AB-ratio with a wide range of signs and symptoms;
- the percentage of PAOD patients had to be large enough to allow selection of a sufficient number of subjects for the 'course & intervention' study;
- in order to be able to correct for selection mechanisms in studying diagnostic relationships, the selection process had to be fully documented.

With these conditions as a starting point, the selection procedure was modified as follows. First of all, the criterion for 'increased risk' was narrowed down: the items 'family history of cardiovascular disease' and 'cold feet' — the least discriminatory, as expected — were excluded from consideration. Five items then remained: pain while walking, smoking of 15 or more cigarettes a day, hypertension, diabetes mellitus, and cardiac complaints or stroke in the past. Consequently, the answers could vary from one to five times 'yes', corresponding with a prior risk score

(termed 'score' below) of 0 to 5.

Secondly, the sample from the group without increased risk (score = 0/5) was reduced to 500. This did not conflict with statistical considerations with regard to the prevalence estimation (research topic 1).

Thirdly, from the group with increased risk (score $\geq 1/5$) an initial random sample of $n = 1000$ was taken for the study on signs and symptoms. From a statistical viewpoint this sample size seemed large enough for research topic 2.

Finally, from the remaining group with increased risk, the 4500 patients at greatest risk were selected. Generally, these patients had a score of $\geq 3/5$; in some practices, additional patients were recruited out of the 2/5 score group. In this way an efficient tracing procedure for the 'course & intervention' study was guaranteed.

Each patient was given a code indicating to which selected subgroup he belonged: 'no risk' (1), 'increased risk' (2), or 'highest risk' (3). This revised selection procedure made it possible to estimate the prevalence both in the total population and in the various selected subpopulations. Moreover, the value of (combined) diagnostic data could be studied in the three subgroups which represent both an increasing level of prior probability and clinical relevance.

For two of the practices the adjusted procedure proved yet too laborious. Therefore, in these two practices only patients from the 'highest risk' group were selected for participation in the PAOD Study. Given the differently selected study population, the patients identified in these practices could be admitted to the 'course & intervention' study, but the data could not be used for the analysis of the 'prevalence & diagnosis' study. Thus, 18 general practices finally took part in the present study (*appendix 5.1*). The modified study design is presented in *figure 5.2*.

In summary, the following populations can be discerned:

- 1 a The *source population*: all subjects who were mailed a postal questionnaire (S)
b The *respondents*: those patients out of S who returned a completed questionnaire (R).
c The *non-responders*: those subjects out of S who did not return the postal questionnaire (NR).
- 2 a The *invited population*: all patients who — on the basis of the sampling and selection procedure — were invited to be examined by their general practitioner (I).
b The *study population*: the patients out of I who actually took part in the study (P).
c The *non-participants*: those patients out of I who did not partake in the study (NP).

Data collection

The invited population

The respondents who were invited to be examined by their general practitioner were divided into three groups. *Group 1* (no risk) consisted of a random sample (500) of all patients belonging to the subpopulation of respondents with a prior risk score of 0/5. *Group 2* (increased risk) comprised patients belonging to the sample (1000) of the subpopulation with a score of 1/5 to 5/5. *Group 3* (highest risk) consisted of those patients (4500) out of the subpopulation with a score of 1/5 to

Figure 5.2 Modified design of the Limburg PAOD Study

1986/87

patients, 1911-1946, male & female,
from 18 general practices
(n= approx. 26000)

1987

POSTAL QUESTIONNAIRE

non-response

symptoms + risk factors	symptoms, no risk factors	no symptoms, risk factors	no symptoms, no risk factors
----------------------------------	------------------------------------	------------------------------------	---------------------------------------

score $\geq 1/5$

score = 0/5

n = 13-14000 increased risk

random sample

n = 500

first a random sample
n = 1000

then a selection of "highly
increased risk"
from the remainder
(score $\geq 3/5$ (n = 4500))

1987/
1989

EXAMINATION IN GENERAL PRACTICES
n = 6000 patients maximally

non-part.

history
physical exam.
patient record

resting AB-Ratio
by means of
pocket Doppler

TOPIC 1: 'PREVALENCE'

1990/91

TOPIC 2: 'CLINICAL DIAGNOSIS'

1987/91

'COURSE & INTERVENTION' STUDY

5/5 who remained after group 2 was formed and who moreover had the highest risk (score 5/5, 4/5, 3/5, and, in some practices, 2/5). The three groups comprised 8.3%, 16.7%, and 75%, respectively, of the total population invited for an examination.

In order to increase the response, the practice assistants were asked to invite the subjects by telephone if possible. In addition, the practices were provided with letters of invitation and letters of reminder with the letterhead of the practice. The assistants were to note the reasons for drop-out on a special form.

Procedure

Data collection in the general practices followed a cross-sectional design, in which at one moment diagnostic data were gathered by means of two methods:

- the '*clinical method*' — history, physical examination and data from the patient record — leading to a clinical diagnosis of the general practitioner including a differential diagnosis, and
- the '*Doppler method*': the measurement of the resting AB-ratio by means of a pocket Doppler device and a mercury sphygmomanometer.

The history was taken by means of a questionnaire, completed by the patient at home and taken along to the appointment. The practice assistant checked the questionnaire for completeness, after which the general practitioner read it. The patient was examined by the general practitioner. A Doppler measurement was performed by the practice assistant.

Clinical and Doppler data had to be collected independently in order to prevent bias by foreknowledge. It would have been ideal if in all cases the Doppler testing had been performed by the practice assistant or a fellow general practitioner, and the clinical part of the study by the patient's own general practitioner. However, it was foreseeable that this would not be possible in all practices and in all cases. Hence, record was kept as to who performed each of the two parts of the study, to allow control for bias.

In cases where the two data collections could actually be carried out independently, the sequence chosen was left to the practices. In those cases where the general practitioner collected both clinical and Doppler data, the Doppler testing was done last. It was presumed that the Doppler measurement would be less sensitive to subjective influences as compared to the physical examination.

In case of at least one AB-ratio < 0.95 an appointment was made with the patient for a second Doppler measurement one week later. Preferably, this second measurement was taken by the same investigator who had done the first.

The studied variables.

The data collected by the general practitioners and their assistants were recorded on registration forms (*appendix 5.3*). These forms came together with a clarification for the general practitioner and with instructions for the general practitioner and the practice assistant. Before the data collection started, the researchers personally went through the protocol with the general practitioners and the assistants.

After a few weeks of experimentation, the majority of practices had found a way of organizing the study that fitted in with their style of practice management: planning appointments with one or more patients in the course of the surgery hour

on suitable days or alternatively, planning several patients on a fixed day in the week.

In the subsequent paragraphs the contents of the various forms will be discussed. *Table 5.1* indicates the various steps that were involved in the process of developing the registration forms.

The patient questionnaire (appendix 5.3)

The aim of the questionnaire was to obtain data from the medical history of the patient on:

- complaints, whether typical for PAOD or not
- a number of risk factors for PAOD
- self-medication, especially of salicylic acid derivatives
- physical exercise

The diagnosis PAOD had to be made or rejected by the general practitioner on the basis of these data plus the data derived from the physical examination and the patient record.

The items of the questionnaire were selected following a study of the literature on the history and pattern of complaints in PAOD (*chapter 2*), and after discussion within the project group. A commentary on the various groups of questions in the patient questionnaire is given in *appendix 5.4*.

The questionnaire was a deliberate compromise between those questions that general practitioners usually ask the patient and the data required for the research project. After all, the study aimed to establish whether complaints mentioned in the literature or considered potentially important by the research team, would be relevant for the general practitioner in assessing a case.

No existing questionnaire was found that would have suited our research topic without substantial adaptation. The 'Rose questionnaire' — a standardized questionnaire for intermittent claudication¹ — though too restricted for the purpose of the study, was incorporated. At the time, no publications had appeared yet on the Edinburgh questionnaire.²

The general practitioners' form (appendix 5.3)

The aim of the general practitioners' form was to obtain data on:

- findings of the physical examination in subjects with and without PAOD;
- risk factors related to PAOD as recorded in the general practitioner's patient records;
- inclusion and exclusion criteria for the 'course & intervention' study;
- the extent to which patients with PAOD were known to their general practitioner.

The items in the general practitioners' form were included after a study of literature (*chapter 2*) and discussion within the project group. The general practitioners were given the opportunity to comment on earlier versions. This questionnaire also became a deliberate compromise between what was current in general practice, what might be interesting to investigate on the basis of literature, and what was considered feasible in a patient and practice bound study. A commentary on the various groups of items of the general practitioners' form is presented in *appendix 5.4*.

Table 5.1 The development of the registration forms

Date	Activity
1986	October
	Literature study and discussion about contents and utilisation of registration forms.
1987	February
	Tentative concept ready.
	March
	Test of draft questionnaire among 9 patients. Written comments of general practitioners on all forms (response: 2/36).
	June
	Professional layout.
	July
	Printing of tentative version.
	August
	Start of study in two pilot practices.
	October
	Analysis of 40 sets of forms. Adjustment of tentative version.
	November
	Oral comments by general practitioners and practice assistants during an informative session for all participants.
	Definitive layout and typesetting.
	December
	Printing of definitive registration forms.
1988	January
	Start of the study in the remaining 16 practices.

The measurement of the resting AB-ratio and the choice of a diagnostic cutoff value (appendix chapter 3)

The function of the Doppler measurement was:

- to determine the prevalence of PAOD in the study population by means of an objective criterion,
- to obtain a standard to which signs and symptoms could be compared
- to select patients for the follow-up study

In review articles that appeared before the study had started (1970 to 1987) it was pointed out that exercise testing was the best way to diagnose PAOD.³⁻¹¹ Three methods qualified:

- the measurement of the course of the AB-ratio after a standardized treadmill test
- idem, after 1-2 minutes of ankle flexion/extension
- idem, during the reactive hyperaemia period following the abrupt release of the sphygmomanometer cuff pressure, applied at a suprasystolic level for 3-5 minutes, proximal to the ankle.

The literature indicates that — in contrast with the flexion/extension method — the reactive hyperaemia test was sufficiently reproducible. In addition, the latter test might be carried out not only in the absence of ECG control but also for both legs separately, which is not the case for the treadmill test. Fowkes, moreover, cautiously advocated the reactive hyperaemia test, although the present study had at the time already commenced.^{12,13} However, this theoretically 'ideal' method requires 30-45 minutes per patient and can be painful. The reproducibility of the test is reported to be inferior to that of the resting AB-ratio measurement.^{13,14}

After discussion within the project group — which included a vascular surgeon — the resting AB-ratio measurement was opted for. This method appeared sufficiently valid for use as 'standard diagnostic test' (chapter 3). According to the literature, the resting AB-ratio permits a clear distinction between angiographically normal vessels and 'significant disease', i.e. occluded vessels.

However, there is an overlap between normal and stenosed vessels. Thus, the choice of the cutoff point in the range between 0.90 (higher specificity) and 1.00 (higher sensitivity) was subject to discussion. Considering the anticipated negative effect of too low a specificity on the predictive value of a positive Doppler test outcome, it was decided to select 0.95 as the cutoff point, this being a balanced compromise between the 'sensitive' 1.00 value and the 'specific' 0.90 value. The following considerations were taken into account:

- With a cutoff point of 0.95, the number of false positive Doppler test results should approximately balance the number of false negative outcomes, which is desirable in terms of the prevalence estimation;
- With a cutoff point of 0.95, fewer subjects would be labelled as patients incorrectly than with a cutoff point of 1.00. Consequently, the study population for the 'course & intervention' study would be less diluted with these false positives, and any effect of calcium carbasalate would be less masked.

In this study the Doppler measurement was carried out according to protocol, preferably by the practice assistant (*appendix chapter 3*). The results of the measurement were recorded on the 'Doppler form' (*appendix 5.3*). The Doppler test was repeated after a week if the AB-ratio was lower than 0.95 for at least one leg. The subject was considered a 'PAOD patient' only, if at this second measurement an AB-ratio of less than 0.95 was again obtained for the leg concerned. The subject was considered not to have PAOD if the AB-ratio was normal for both legs at the initial measurement.

Before the data collection started, informative sessions were held for the general practitioners and their assistants, and a reproducibility measurement was organized in order to determine the inter-observer variability of the resting AB-ratio measurement. The patients for this reproducibility measurement were recruited from the outpatient population of a vascular surgeon of the University Hospital Maastricht. All practice mercury sphygmomanometers were calibrated during these sessions as well.

Data processing and analysis

The researchers visited each practice at four- to six- week intervals in order to check on the course of the project, to discuss problems and to collect questionnaires. The general practitioners were kept informed about the progress via regular newsletters.

The registration forms were checked for completeness by the practice assistants and the researchers. Forms that were incomplete or erroneously filled in were returned to the practice with a request for completion and/or correction.

All data were coded by the research assistants. They were typed onto punch cards by two data typists working independent of each other. The punch cards were read into the university's mainframe computer, which compared the corresponding codes. Dissimilar sets of codes were thus identified and corrected.

The data were analyzed with the software programme BMDP (BMDP Statistical Software Inc., 1988/1990). The ultimate analyses were preceded by analyses on the incomplete data base to detect inconsistencies and gaps in the various data files and the BMDP operator programme, to practise with various BMDP analysis programmes, to see whether the collected data would indeed yield plausible and useful

results and to prepare presentations of preliminary results.¹⁵⁻²¹ Additions, transformations and corrections of the data base that later proved necessary were read into the data base on screen by the research assistants. The analysis was further designed as follows:

- *Account of the selection process as it occurred in actual fact.* The various populations were described with regard to relevant variables (age, gender, score, group). Non-response and non-participation were also described in qualitative and quantitative terms. The methods and outcomes of these analyses are presented in *chapter 6*.
- *Determination of the prevalence of the various manifestations of PAOD by gender and by age category.* The prevalence in the source population was determined by calculating back from the figures obtained for the selected study population. The methods and results of these analyses are discussed in *chapter 9*.
- *Analysis of diagnostic relationships.* The sensitivity, specificity predictive values were assessed separately for each diagnostic variable. Subsequently, the diagnostic value attained by combined diagnostic data was assessed. Multivariable logistic regression analyses was used. The methods and results of these analyses may be found in *chapter 10*.

Additional studies: the measurement and interpretation of the AB-ratio

A study on the *reproducibility* of the AB-ratio was organized in the spring of 1987. The magnitude of different sources of measurement variation, relevant to clinical practice as well as multi-observer studies, was estimated from a random effects analysis of variance model. Thirty-five GPs and 24 practice assistants — joining in the Limburg PAOD Study — performed 503 AB-ratio measurements on nine patients over a period of nine weeks, using pocket Doppler devices. Methodology and results of this study will be discussed in *chapter 7*.

In the spring of 1991 a *validity* study was undertaken in which the diagnostic outcome of the measurement of the AB-ratio in three general practice centres — participating in the Limburg PAOD Study — was compared to the diagnostic conclusions of the Vascular Laboratory of the University Hospital in Maastricht. This was done both for the outcome of single AB-ratio measurements (231 legs of 117 patients) and the outcome of measurements on three consecutive occasions (subgroup of 92 legs of 51 patients). Methodology and results of this study will be described in *chapter 8*.

Ethical aspects

The participation of the patients in the postal inquiry and the examination in the general practices was voluntary. The patient was aware of the noninvasive nature of the Doppler testing. He was guaranteed explicitly that non-participation would not influence the normal relationship with his general practitioner.

The registration forms were provided with cover pages on which the personal details of the patient and an identification number were recorded. These cover pages were removed from the forms after they had been checked for completeness. The personal details — including the identification number — were then entered into a

database in the project's personal computer, and used for administrative purposes (letters to patients, overviews for the general practitioners, address stickers, etc.).

The completed and coded registration forms were kept in lockable filing cabinets in the project's office, which is closed after working hours. The anonymous and coded research data were processed by means of the university mainframe computer. The identification number was used to keep together the data of each patient, and, if necessary, to examine the personal details data file in the personal computer.

The 'Limburg PAOD Study' was approved by the Medical Ethics Committee of the University of Limburg and the University Hospital Maastricht, on 22 May 1987.

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Chapter 6 Selection process and populations*

Summary This chapter presents a quantitative overview of the processes of selection and drop-out that led to the definitive study population. The extent of selective drop-out is assessed. Finally, the study population is described for a number of key parameters.

The source population consisted of 26620 patients with a mean age of 56.5 years (range: 40.3-76.9 years) of whom 52.5% were female. The overall response on the postal questionnaire was 86.4%. The average response rate per practice was 85.7% (SD: 3.4%). The non-response did not cause a significant selective drop-out by age or gender.

There were 9095 responders with a prior risk score of zero and 13909 responders with a score from one to five. From the population of responders two random samples were taken: from the category with a score of zero (group 1, 'no risk', $n = 451$) and from the category with a score of one to five (group 2, 'increased risk', $n = 897$). Both samples proved to be representative for their respective source populations with regard to age and gender. Of the remaining patients with a score between one and five, those at highest risk were selected (group 3, 'high risk', $n = 3953$).

Thus, 5301 subjects were invited for an examination in one of the 18 general practice centres. The invitation was accepted by 68.9%. The average participation rate per practice was 70.2% (SD: 11.9%). Non-participation was due to various reasons: patients stayed in hospital for a protracted period or had moved or had died (17.5%); many patients were 'not interested' (48%); sometimes general practitioners decided that a patient would not participate for medical or practical reasons (11%). The remaining causes for non-participation were unknown (23.5%). The non-participation was selective to a certain degree for 'age' (older age groups), 'gender' (males), and 'score' (inconsistent pattern).

The definitive study population comprised 3654 patients (group 1: 292; group 2: 626; group 3: 2736) aged 40.7-78.3 years (mean age: 59.1 years) of whom 53.0% were female.

Introduction.

In chapter 5 the design, populations, methods and variables of the study were described. The present chapter discusses the selection process as it actually occurred. Subsequently, the extent of selective drop-out is examined. Finally, the definitive study population is described with reference to a number of key characteristics. These analyses are essential in order to identify any bias in the results. In addition, they may help the general practitioner to decide on the significance of the results for his particular practice.

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Methods

To determine whether selective drop-out occurred, populations were compared on two levels:

- level 1: source population (S) versus responders (R) and non-responders (NR) (see *chapter 5*);
- level 2: invited population (I) versus study population (P) and non-participants (NP) (see *chapter 5*).

In addition it was checked whether the sampling procedure had been successful.

Level 1: source population, responders, non-responders

It was examined to what extent selective drop-out occurred with respect to the variables 'age' and 'gender'. This is relevant for the prevalence computations, and thereby indirectly for the analysis of the diagnostic value of data from the history and physical examination. A chi-square test was used to investigate the hypothesis that the distribution over age and gender categories of the NR and R populations is similar.

Sampling procedure

To assess in how far the random samples from the population of responders with a score of 0 (random sample = group 1) and 1-5 (random sample = group 2) were representative for their respective source populations, the distributions of 'age' and 'gender' were compared. The subpopulation of R with score = 0 was compared to its sample, group 1, and the subpopulation of R with score = 1-5 was compared to its sample, group 2. The chi-square test was used for assessing statistical significance.

Level 2: invited population, study population, non-participants

It was examined to what extent selective drop-out had occurred with respect to the variables 'age', 'gender', 'group', and 'score'. A chi-square test was used to investigate the hypothesis that the distribution over the various categories of these variables in the NP and S populations is similar. The reasons for non-participation were classified into ten categories. The study population was described for a number of key characteristics: age, gender, score, group, and co-morbidity.

Statistical Software

The programme BMDP (BMDP Statistical Software Inc., 1988/1990) was used to describe the age distribution in various populations. Confidence intervals (95%) of proportions were calculated with the programme CIA (CIA, version 1.0, British Medical Journal & MJ Gardner, 1989). In most cases, the BMDP programme was used to calculate the Pearson chi-square tests and the corresponding p-values. The spreadsheet programme Lotus (Lotus 1-2-3, release 2.2, Lotus Development Corporation, 1989) was used for determining the Pearson chi-square test in respect of the representativeness of the sampling procedure; the corresponding p-values were computed with the Epistat programme (True Epistat, Epistat Services, 1987).

Figure 6.1 Selection procedures and populations

Population level 1

age¹: age at time of postal inquiry
age²: age at time of examination in GPCs

Results

The selection process

In *figure 6.1* the successive phases of the selection process are quantified for the most important parameters. The response to the postal questionnaire was 86.4%. The average response percentage per practice was 85.7% (SD = 3.4%, range = 76.0-90.4%).

From the category of responders with score = 0, a random sample was taken (group 1). From the category of responders with a score of one to five also a random sample was taken (group 2). Of the remaining patients in this category (n = 13012) 30.4% were in the 'highest risk' group (group 3). Altogether, 23% of the responders were invited for an examination by their general practitioners (n =

5301). The percentage of patients that subsequently participated amounted to 68.9% of the invited population. The average participation percentage per practice was 70.2% (SD = 11.9%) of the invited practice population. Two practices had a relatively low participation level (38.1% and 47.7%, respectively) whereas two other practices had a relatively high participation level (83.8 and 89.8%, respectively).

Non-response on population level 1 (S-R-NR)

The age distributions of NR, R, and S correspond very closely (*appendix 6.1*). In the highest age category a significantly greater percentage non-responders is found (*appendix 6.2*). Comparison of the gender distribution of the three populations (*appendices 6.3a, 6.3b*) indicates that the gender distribution of NR does not differ significantly from the gender distribution in R and S. The percentage of non-responders among men does not differ significantly from that among women (*appendix 6.4*).

Representativeness of the sampling procedure

The two random samples from R (see *figure 6.1*) are representative in terms of age and gender for the respective populations from which they were drawn (*appendix 6.5*). According to the chi-square tests, the minimal deviations of the sample fractions per age category as well as the slight overrepresentation of women in both samples are not significant.

Non-participation on population level 2 (I-P-NP)

In order to identify any age-specific drop-out, it was examined in how far patients from NP and P differed both in comparison to each other and in relation to I regarding the distribution of the variable 'age at time of postal inquiry' (*appendix 6.6*). On the average non-participants were almost 2 years older than participants. The non-participation percentage per age category was also assessed (*appendix 6.7*). The participation rate of subjects aged 45 to 65 was higher than average, whereas in subjects older than 65 it was lower. Although women participated more than men, the gender distribution of NP and P did not differ significantly from that in I (*appendices 6.8 and 6.9*).

The participation by score and group is represented in *appendices 6.10 and 6.11*, respectively. The distribution of 'score' in the three populations reveals a varying pattern: in the categories with score = 0, 3, and 4 the drop-out was more than average, whereas in the category with score = 2 the drop-out was less. Although the drop-out in the group without increased risk (group 1) was more than average, the distributions of 'group' in I, P, and NP are comparable.

Table 6.1 indicates for what reasons patients did not participate. In 17.5% of cases this was because the period between postal questionnaire and the examination by the general practitioner had lapsed: some subjects had moved, others had died, or were absent due to protracted hospital admission (reasons 1-3). In almost half of all cases the patient was 'not interested' in the study (reason 4). In 11% the general practitioner decided that the patient would not participate (reasons 5-8). For the remaining quarter of the non-participation the reason remained unknown or was due to administrative errors (reasons 9 and 10).

On the average, the lapse of time between the completion of the postal questionnaire and the GP's examination was one year (SD = 0.42 year, median 0.9 year $\approx$

Table 6.1 Reasons for not participating. Percentages of total number of non-participants (n = 1647)

	Reason for not participating	% of non-participants
1	Patient had moved	9.0
2	Patient had died	7.3
3	Patient had been transferred to hospital or nursing home or psychiatric centre	1.2
4	Patient was not interested in study, had no time or did not keep appointment	48.0
5	GP excluded patient because of medical, psychological or social 'contra-indications' ('research would harm patient')	1.3
6	GP excluded the patient because in his opinion the patient was not suited to participate in research, e.g. non-compliance ('patient would harm research')	0.5
7	GP excluded the patient because the patient could not come to the GPC (not mobile, living in home for the elderly etc.)	5.5
8	GP failed in reaching the patient (e.g. secret phone number)	3.4
9	Unknown reasons	23.0
10	Error by GPC or research team	0.9
	Total	100.0

11 months); this 'investigation delay' ranged from 0.29 year (3.5 months) to 2.16years (26 months).

The study population

The composition of the study population (n = 3654) in terms of gender (53% female), group (group 1, 'no risk': 292, group 2, 'increased risk': 626, group 3, 'highest risk': 2736), and score may be found in column 'P' of *appendices 6.8, 6.10, and 6.11* respectively. The age distribution of the study population is depicted in *table 6.2*. The mean age ('age at examination') in the study population is 59.1 years and the median 59.3 years. The age ranges from 40.7 to 78.3 years. Among subjects between 40 and 65 years of age men are somewhat overrepresented, among subjects over 65 women are. Finally, *the tables 6.3 and 6.4* provide an overview of relevant co-morbidity in the study population.

Discussion and conclusion

A high percentage of patients returned the postal questionnaire (86.4%). In accordance with this high response, the population of responders is comparable to the source population in terms of age and gender distribution. This means that age- and gender-dependent associations that are found in the population of responders (R) may be extrapolated to the source population (S).

The samples 'group 1 (no risk)' and 'group 2 (increased risk)' are representative with respect to age and gender for the populations from which they were taken: the responders with score = 0 and score = 1-5, respectively.

Table 6.2 Age & gender distribution in the study population

Age category	Male (%)	Female (%)	Total _{age} (%)
40 ≤ 45	157 (9.2)	162 (8.4)	319 (8.8)
45 ≤ 55	481 (28.0)	499 (25.9)	980 (26.9)
55 ≤ 65	602 (35.1)	645 (33.4)	1247 (34.2)
65 ≤ 75	410 (23.9)	526 (27.3)	936 (25.7)
> 75	65 (3.8)	98 (5.1)	163 (4.5)
N	1715 (100.0)	1930 (100.0)	3645 (100.0)
Missing _{age}	4	5	9
Total _{gender}	1719 (47%)	1935 (53%)	3654 (100%)

The participation percentage, 68.9% of the invited population, is considerable. In contrast with the response to the postal questionnaire, there was a large variation between practices with respect to degree of participation. According to the reports of the practices, only a small percentage of the drop-out (11%) was partly influenced by the factor 'general practitioner'. However, in three-quarters of all cases, the reason for drop-out was in fact unknown ('not interested', 'unknown', 'mistake'). The variation in these categories possibly indicates that differences related to practice management and attitude to scientific research played a role. The study data do not seem to suggest that this variation led to bias in the study population as a whole.

Older patients are overrepresented among the non-participants. Consequently, the average age of the participants decreased relative to the invited population as a whole.

Owing to the time period taken by the study, an 'investigation delay' of one year on average arose, and ultimately the mean age of the study population was higher than of the invited population. Hence, age-dependent associations will have to be evaluated per age category. For the calculation of prevalence figures this is desirable for other reasons as well: the youngest and oldest age categories ($40 \leq 45$ years and $75 \geq 80$ years) will be excluded from the analysis due to their relative underrepresentation in the study population as compared to the population of responders.

The participation of men was lower (32.3% drop-outs) than that of women (30.0% drop-outs). However, there are no significant differences in the gender distribution of the non-participants, participants and invited population. Nonetheless it is desirable to evaluate gender-dependent associations for men and women separately in order to increase or reduce the plausibility of any existing differences between men and women.

The pattern of drop-out per 'score' category was somewhat variable: in the score = 0, 3, and 4 categories the degree of participation was lower, whereas in the score = 2 category it was higher than average. This means that the prevalence figures are best computed by means of the frequency per score category; this method is also the most precise and efficient (see *chapter 9*).

Looking at the drop-out per 'group', one notices a smaller degree of participation in the group 'no risk' (group 1) than in the other two groups. The distribution of 'group' of non-participants, participants and invited population is similar, however.

Table 6.3 Cardiovascular morbidity in the study population (n=3654, f= 53%, age 40.7-78.3 years)

Diagnosis	Prevalence in %
Angina pectoris, coronary ischaemia	19.0
Myocardial infarction	12.8
Transient ischemic attack, carotid stenosis	3.6
Stroke	2.7

Table 6.4 Leg diagnoses in the study population (n = 3654, f = 53%, age 40.7-78.3 years)

Diagnosis	Prevalence ^a	
	GP's diagnosis 'PAOD highly probable/possible' [n = 653] ^b : concomitant leg disorders (%)	GP's diagnosis 'PAOD not probable' [n = 2980] ^b : differential diagnosis (%)
Raynaud, B�rger, chilblained feet	2 (0.03)	16 (0.5)
Varicose veins, venous insufficiency, venous ulcer	89 (13.6)	417 (14.0)
Osteoarthritis of hip, knee, ankle and leg n.o.s. ^c	67 (10.3)	319 (10.7)
Peripheral neuropathy, neuralgia, sciatic pain, lumbar disc lesion,	44 (6.7)	207 (6.9)
Restless legs, paraesthesia	13 (2.0)	93 (3.1)
Pain, cramps and other complaints of legs n.o.d. ^d	13 (2.0)	246 (8.3)
No (other) leg problems	420 (64.3)	1682 (56.4)

^a the sum of percentages exceeds 100% since patients may have more than one diagnosis

^b missing values in 21 patients

^c not otherwise specified

^d not otherwise defined

For the calculation of prevalence figures, the noted difference is of no consequence, since the variable 'score' will be used for calculating backwards. With respect to the analysis and interpretation of diagnostic relationships it may be important that the study population as a whole is at a slightly higher risk. Considering that the variable 'group' can be viewed as an operationalization of 'level of selection', it would be interesting to determine diagnostic associations per 'group' as well.

The 'investigation delay' may have led to an increase of the risk score due to (co-)morbidity: 'complaints while walking', 'diabetes mellitus', 'hypertension', and 'a history of cardiovascular disease' may have become relevant in the meantime. The mean score per group may thus be somewhat higher than measured.

In summary, it may be observed that there are no indications that significant selective drop-out occurred: the differences that arose are minimal. Nevertheless, these differences will be taken into account as much as possible in the analyses.

Chapter 7 The reproducibility of the ankle-brachial systolic pressure ratio*

Summary One of the noninvasive techniques used in the diagnosis of patients with peripheral arterial occlusive disease is the measurement of the ankle-brachial systolic pressure ratio ('AB-ratio').

The magnitude of different sources of measurement variation, relevant to clinical practice as well as multi-observer studies, was estimated from a random effects analysis of variance model. Thirty-five general practitioners and 24 practice assistants performed 503 AB-ratio measurements on nine patients over a period of nine weeks, using pocket Doppler devices.

When the AB-ratio is used for diagnostic purposes, a 95% prediction interval consisting of the measured value ± 0.15 - 0.20 has to be taken into account.

Furthermore, when the AB-ratio is used in the follow-up of a patient with vascular disease, the difference between two subsequent measurements has to be at least $0.16 - 0.19$ to have an 80% certainty that this difference is not due to (intra-observer) measurement error.

Key words peripheral arterial occlusive disease, general practice, epidemiology, diagnosis, ultrasound.

Introduction

Peripheral arterial occlusive disease of the lower limbs ('PAOD') is the manifestation of atherosclerosis in the arteries below the aortic bifurcation. In a general practice population, the prevalence of intermittent claudication (i.e. cases of whom the general practitioner is aware) has been reported to be three to seven per thousand.¹ It can be estimated from population screening studies that this figure rises to 25 per thousand if asymptomatic and unknown cases of PAOD are allowed for as well.^{1,2}

Over the last two decades noninvasive techniques have become a major tool in the diagnosis of PAOD. Vascular laboratories offer sophisticated diagnostic possibilities to the vascular surgeon.^{3,4,5} One of these techniques, which is based on the use of ultrasound, is the measurement of the ankle-brachial systolic pressure ratio (AB-ratio), reflecting the functional state of the circulation in the lower limbs.⁶ Most suited for use in general practice and in epidemiological research on PAOD is the pocket-sized Doppler device which is used like a stethoscope together with a

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mercury sphygmomanometer ('Doppler method'). Since the predictive value of 'classic' signs and symptoms that are indicative of PAOD is not very high,⁷ the Doppler method may be useful in establishing the diagnosis 'PAOD'.¹ An AB-ratio larger than 1.0 indicates that there is no PAOD, while an AB-ratio smaller than 0.90 strongly suggests PAOD.^{4, 8-10}

Although the diagnostic validity of the method in cross-sectional research is reported to be good if a cut-off value of 0.90 is used,^{8,9,11,12} the interpretation of data on the reproducibility of the AB-ratio is difficult and results cannot easily be generalized to general practice (i.e. general practitioners and their practice assistants).^{3,8,13-18} The Department of General Practice of the University of Limburg is currently investigating some aspects of PAOD relevant to general practice such as prevalence, diagnosis, natural course, and therapeutic interventions (the 'Limburg PAOD Study').¹ The resting AB-ratio, measured with a pocket Doppler device, is used as the standard diagnostic procedure and as one of the outcome measures.

Because of the forementioned uncertainty regarding the reproducibility of the AB-ratio, a study was conducted with the primary intention of estimating the magnitude of measurement variation due to the multi-observer design of the 'Limburg PAOD Study'. A secondary intention was to obtain information on other sources of measurement variation, relevant to clinical situations.

Material and methods

Patients

Four male and five female patients, aged 47-74, participated in the study. *Table 7.1* shows the selection pattern and the clinical characteristics of the patients.

Observers

Fifty-nine observers (35 general practitioners, 24 practice assistants), participants in the forementioned 'Limburg PAOD Study', cooperated in the study. They participated in a Doppler training course. At the start of the reproducibility study, the observers had all been using Doppler devices in their own practices for some nine months.

Measurements

For practical reasons we had to divide patients into two groups, the 'Wednesday' (patients A-E, measured on four Wednesdays) and the 'Thursday' group (patients F-I, measured on five Thursdays) (see *table 7.1*). For each 'measurement day' there were four to nine observers, who each measured four or five patients. The interval between the first and last measurement day was eight or nine weeks. The interval between two consecutive measurement days was one or two weeks. The time between the first and last measurements on one day varied between two and three hours.

8 MHz pocket-sized Doppler devices (Hundleigh D500) and calibrated mercury sphygmomanometers, cuff size 12 cm, were used for both ankle and arm measurements. The patients were lying supine, each in a separate, heated room. The observers were unaware of any detail of the medical history of the patients. Each individual observer measured systolic pressures of the left arm (brachial artery) and the left and right ankles (posterior tibial artery or dorsalis pedis artery). The obser-

Table 7.1 Patients

Patient	Gender	Age	Diagnosis [and location of vascular diagnosis]	Vascular surgery
A	F	66	intermittent claudication R > L [vascular laboratory]	–
B	F	58	arthrosis knee and hip [GP: AB-ratio L+R > 1.0]	–
C	F	56	intermittent claudication R [GP: AB-ratio R absent, L 0.50]	–
D	F	47	intermittent claudication L > R [vasc. laboratory/arteriogr.]	+
E	M	50	no leg complaints [vasc. laboratory /arteriogr.]	+
F	M	74	myalgia, sciatica [GP; AB-ratio not available]	–
G	F	73	intermittent claudication R > L [vascular laboratory]	–
H	M	68	intermittent claudication L+R [vascular laboratory]	+
I	M	69	intermittent claudication R [vascular laboratory]	–

M= male, F= female, L= left, R= right, GP= general practitioner

vers changed rooms after twenty minutes and they were not allowed to exchange results. Two authors (HSt, VK) supervised the whole procedure.

Statistical analysis

Apart from the inter-patient variation, the variation in measured AB-ratios can be attributed to different sources:

- 1 The AB-ratio of one patient varies from day to day. This long-term biological variation was subdivided into the variation which is common to both legs (the analysis of variance term for this component is 'patient by day') and in the remaining biological variation: the difference in variation between both legs (called 'leg by patient by day').
- 2 Observers exhibit different systematic measurement variation, observer bias ('observer').
- 3 The remaining measurement error comprises two components. First, error common to the measurements of both legs ('patient by observer') and second, the residual error ('residual'), including any short-term biological variation as well as a possible interaction ('leg by patient by observer') that occurs when the error of an observer is systematically different for different legs.

The long-term biological variation, observer bias, and both components of the remaining measurement error were estimated from a random effects analysis of variance model.^{19,20} Results are presented as estimated variances. From these variances, measurement variation SDs and 95% prediction intervals were computed

Table 7.2 Measurements, mean AB-ratios and standard deviations

Patient	Leg L/R	Number of measure- ments	Number of measure- ment days	Mean AB-ratio	Standard Deviation (pooled)
A	L	21	4	0.82	0.081
	R			0.70	0.081
B	L	22	4	1.05	0.111
	R			1.19	0.125
C	L	22	4	0.82	0.190
	R			0.74	0.133
D	L	22	4	0.66	0.072
	R			0.67	0.124
E	L	20	4	1.07	0.128
	R			1.10	0.211
F	L	37	5	0.66	0.112
	R			0.56	0.093
G	L	35	5	0.69	0.082
	R			0.65	0.100
H ^b	L	20	3	0.85	0.109
	R			0.79	0.109
I	L	36	5	0.83	0.096
	R			0.79	0.101
H ^b	L	7	1	0.36 ^a	0.077 ^a
	R	8		0.67 ^a	0.068 ^a
E ^b	L	9	1	0.74 ^a	0.101 ^a
	R			0.73 ^a	0.113 ^a

^a Day-mean and day-SD.

^b On his fourth measurement day, patient H appeared to be suffering from severe pain in his left leg, which corresponded well with a dramatic fall in his AB-ratio (H' in the table). Therefore, on the fifth measurement day patient H was replaced by patient E (=E').

for various situations.

Results

Table 7.2 summarizes the results of the pressure measurements. The total number of AB-ratio measurements was 503. The standard deviations of individual legs varied between 0.068 and 0.21 with a mean of 0.11. *Table 7.3* presents the results of the

Table 7.3 Components of variation: estimated variances and standard deviations (SD)

Source	Estimated variance (s.e.)	Estimated SD
Long term biological variation ^a		
- patient by day	0.812 (0.297)	0.090
- leg by patient by day	0.109 (0.065)	0.033
Variation due to the measurement process		
- observer	0.196 (0.077)	0.044
- patient by observer	0.390 (0.089)	0.062
- residual ^b	0.705 (0.069)	0.084

s.e. standard error

^a patients H, H' and E' excluded (see Table 7.2)

^b including short term biological variation and 'leg by patient by observer')

Table 7.4 Total measurement variation SDs and 95% prediction limits for mean AB-ratio under various conditions

Condition	Total measurement variation SD	95% Prediction limits of AB-ratio (AB-ratio $\pm$...)
1 observer, 1 measurement	0.114	0.223
1 observer, 2 measurements	0.097	0.190
1 observer, 3 measurements	0.091	0.178
2 observers, 1 measurement each	0.080	0.157
2 observers, 2 measurement each	0.069	0.135

* The calculations assume that repeated measurements by the same observer have the same 'patient by observer' error and also that the 'residual' errors are independent. This may be accomplished by the use of a random-zero sphygmomanometer.

analysis of variance. The observer bias was low in comparison with the other two components of variation due to the measurement process. *Table 7.4* presents measurement variation SDs and 95% prediction intervals for different situations. For the first condition ('one observer, one measurement') the variance is equal to the sum of the variances of the three components of variation due to the measurement process (see *table 7.3*). Therefore, the SD of the variation in a single measurement of the AB-ratio by one of the 59 observers, which is the inter-observer error SD, equals 0.114. This means that the true AB-ratio is within 0.223 units from the observed value (95% pre-diction limits). Further entries in *table 7.4* show how the interval improves when multiple measurements are taken.

The intra-observer error SD was estimated from the applied random effects analysis of variance model. The intra-observer error SD of the AB-ratio was not larger than 0.105, yielding a 95% prediction interval of the measured value $\pm$ 0.206.

Discussion

We studied the reproducibility of AB-ratio measurements by general practitioners and their practice assistants using pocket Doppler devices, in order to determine its usefulness in a multi-observer epidemiological study. Therefore, determination of the inter-observer error was our primary goal. Our estimate of the inter-observer error SD (0.114, 95% prediction interval $\pm$ 0.223) agrees with other research workers, even though they used different study designs and statistical techniques.^{15,18}

The observer bias appeared to be relatively low. This implies that a multi-observer epidemiological study will be only slightly less efficient than a hypothetical single-observer study with the same number of patients. *Fowkes et al.* drew a similar conclusion.¹⁸

In a single-observer situation, e.g. a general practitioner's practice, the so-called intra-observer error is of interest. This is the measurement variation pertinent when observations are only to be compared with (previous) observations by the same observer. *Buth* reported an intra-observer error SD (including short-term biological variation) of 6.5% of the mean of two measurements on one day.³ From *Fowkes'* detailed analysis of variance components, intra-observer error SDs can be calculated as 0.072 (diseased) and 0.104 AB-ratio (normals).¹⁸

To obtain a direct estimate of the intra-observer error, ideally one needs independent repeated measurements of the same patient by the same observer. This can be achieved using random-zero sphygmomanometers.¹⁸ As the determination of the intra-observer variation was not our primary intention and the random-zero sphygmomanometers were not readily available at the time, we did not use them in this reproducibility-study. Nevertheless, the intra-observer error (including short-term biological variation and 'leg by patient by observer' interaction) could be estimated indirectly from the forementioned random effects analysis of variance model. Conceptually in such a model the intra-observer error is obtained by comparison of the measurement error in different patients measured by one observer. Since the observer bias will be the same with every patient measured by this observer, the observer bias cancels out in the comparison.

The intra-observer error SD of the AB-ratio being 0.105 implies that when the Doppler method is used in the follow up of vascular patients, the difference between two subsequent measurements (of the same patient by the same observer) has to be at least 0.29, before one can be sure with 95% certainty that the observed difference is not due to (intra-observer) measurement error. When two measurements are taken on each occasion, this difference would have to be at least 0.24. If one accepts a lower degree of certainty, e.g. 80%, the minimum significant differences between consecutive occasions can be calculated as 0.19 (one measurement) and 0.156 (two repeated measurements) respectively.

It can be concluded that the Doppler method is suitable for diagnostic purposes in a clinical setting (e.g. general practice) as well as for epidemiological research. The measurement of the AB-ratio is a reproducible and valid technique to make the diagnostic decision whether PAOD is present or not, under the condition that a 95% prediction interval of 0.15-0.20 around the measured value of the AB-ratio is taken into account. Repeated measurements should be taken to minimize the measurement variation and to enhance the diagnostic conclusion.

Using the intra-observer error SDs from this study and others,^{3,18} it can be concluded that the difference between measurements (of the same patient by the same observer) on two subsequent occasions has to be at least 0.12-0.20 to have an 80% certainty that this difference is not due to (intra-observer) measurement error. This conclusion is important if the Doppler method is used in the follow-up of patients treated for PAOD. This conclusion is more relevant to epidemiological research, in which the AB-ratio is an outcome measure, than to clinical practice where the complaints of the patient are the main factor in medical decision making.

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Chapter 8 The diagnostic power of the measurement of the ankle-brachial systolic pressure ratio in general practice*

Summary *The general practitioner has to rely on history taking and physical examination when he wants to diagnose peripheral arterial occlusive disease (PAOD). However, the positive predictive values of these diagnostic procedures do not seem to be very high. In this respect the hand-held Doppler device could be an asset to general practice.*

We assessed the accuracy and diagnostic value of the ankle-brachial systolic pressure ratio (AB-ratio), estimated the optimum cutoff value for the AB-ratio and estimated threshold cutoff values beyond which PAOD can be ruled in or out. The diagnostic outcome of the measurement of the AB-ratio in three general practice centres was compared to the diagnostic conclusions of a Vascular Laboratory. This was done for the outcome of single AB-ratio measurements (231 legs of 117 patients) and the outcome of measurements on three consecutive occasions (subgroup of 92 legs of 51 patients).

Receiver Operating Characteristic analysis showed that the diagnostic value of the mean of three AB-ratios is better than that of a single AB-ratio. The best theoretical optimum cutoff value was a mean AB-ratio of 0.92 (sensitivity 87%, specificity 91%, LR+ 10, LR- 0.14). Accuracy, corrected for prevalence, was 90%. We estimated that the positive predictive value $\geq 95\%$ if the mean of three consecutive AB-ratios is below 0.88; the negative predictive value $\geq 99\%$ if the mean AB-ratio is above 0.98 (prevalence range 5-33%).

Key words *peripheral arterial occlusive disease, diagnosis, ultrasound, general practice, clinical epidemiology*

Introduction

Regarding the diagnosis of peripheral arterial occlusive disease (PAOD) vascular laboratories offer various sophisticated noninvasive ultrasound techniques to the vascular specialist.^{1,2-6} On the other hand, the general practitioner still has to rely on history taking and physical examination as major tools for establishing the diagnosis of PAOD. According to the literature, however, the positive predictive values of intermittent claudication, diminished peripheral pulses or a femoral bruit do not seem to be very high.^{7,8} In this respect the hand-held Doppler device could be an asset to general practice. This simple instrument already exists for many years, but

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has only recently been introduced in general practice.⁹ In combination with a sphygmomanometer it can be used to measure systolic blood pressures.¹⁰⁻¹² The ankle-brachial systolic pressure ratio (AB-ratio) provides a measure of the functional state of the circulation in the lower limbs and normally is above 1.0 in healthy persons.¹³ The measurement of the resting AB-ratio by means of a Doppler device will be called 'Doppler method' hereafter.

Measuring the AB-ratio is appropriate in case of a mobile patient with leg complaints of whom medical history and physical examination do not yield unequivocal results. It is also relevant in case of a patient whose mobility is impaired due to other causes (e.g. cardiac, respiratory, arthritis) and who has leg complaints when resting.^{9,14}

The measurement of the AB-ratio is considered to be a well-researched technique. However, a systematic review of literature^{9,14} revealed that most studies on the validity of the method had been conducted in rather selected study populations.^{2,15-26} In a specialist setting many PAOD cases will be in a more developed stage than in general practice and the validity of the Doppler method in general practice may be different from the validity in referred populations.^{27,28} Moreover, in only six studies a 'gold standard' had been applied to PAOD-cases and non-cases.^{2,15,20-23} Also, it was often not clear whether test and standard procedure had been performed independently from each other.

Which cutoff value for the AB-ratio is considered best depends on whether a high sensitivity or a high specificity is preferred. From the above-mentioned literature an AB-ratio of 0.90 emerges as the 'specific' cutoff point whereas 1.00 is the 'sensitive' cutoff value.^{9,14} Correspondingly, in recent epidemiological studies on the prevalence of PAOD, cutoff values for the AB-ratio mostly were chosen in the range between 0.90 and 0.97.²⁹⁻³³ To medical practice the positive and negative predictive value (PV+ and PV-) of the measured AB-ratio are more relevant than a fixed cutoff value. The literature provides no data on this subject.

The aims of the present study were to assess the accuracy and diagnostic value of the pocket Doppler AB-ratio, to estimate the optimum cutoff value for the AB-ratio, and to provide threshold cutoff values beyond which PAOD can be ruled in (high PV+) or out (high PV-).

Method

Design

In the present study the diagnostic outcome of the measurement of the AB-ratio in three general practice centres (GPCs) using a hand-held Doppler device ('test') was compared to the diagnostic conclusions of the Vascular Laboratory (VL) of the University Hospital in Maastricht ('standard'). This comparison was made for the outcome of single AB-ratio measurements and for the outcome of measurements on three consecutive occasions.

Patient selection

The 'Limburg PAOD Study' is a research project on peripheral arterial occlusive disease conducted by the University of Limburg in Maastricht and 22 general practice centres in the region. In the first part of this project data on signs and symptoms of PAOD were collected among 3654 patients.³⁴ The second part of the

Limburg PAOD Study is a randomised clinical trial among identified PAOD-cases on the effect of aspirin in PAOD.

Using the database of the first part of the Limburg PAOD Study, patients of three participating GPCs in Maastricht were selected. The objective was to create a case-mix with a spectrum relevant to the diagnostic situation of the general practitioner. The following criteria were used: at that time an AB-ratio lower than 0.95 (78 patients); at that time an AB-ratio of 0.95 or higher with either complaints of typical intermittent claudication (IC)³⁵ or with leg complaints less typical for IC but with one or more absent foot pulses (84 patients).

Measurements in the GPCs

Hundred seventeen patients (51 male, 66 female; age 44-80, mean 62.5 years) agreed to participate. They filled in a modified version of the WHO-questionnaire³⁵ assessing current complaints of IC. The patients' records were examined for IC, vascular surgery and relevant co-morbidity. In the GPCs the (six) practice assistants assessed systolic blood pressures on both arms and ankles with the patient lying in supine position, using a hand-held Doppler device (Huntleigh Mini Dopplex D500, 8 MHz). On the average each practice assistant had performed Doppler measurements in more than 200 patients (range 118-339) during the last three years.

In a subgroup of 54 patients (30 male, 24 female; age 44-79, mean 65.6 years) admitted to the second part of the Limburg PAOD Study, results of previous Doppler measurements were available (once in four months). Of these patients the last three AB-ratios before the visit to the VL were averaged for each leg. This mean of three consecutive AB-ratios was also compared to the VL outcome. Legs with consecutive AB-ratios showing a continuous decrease or increase exceeding 0.20, were excluded. Such a trend indicates a clinically relevant change in the course of the disease for this leg.³⁶⁻³⁹

In the GPCs participating in the Limburg PAOD Study an AB-ratio lower than 0.95 was considered a positive outcome. This cutoff value was chosen as a balance between the 'specific' cutoff value of 0.90 and the 'sensitive' cutoff value of 1.0, as reported in the literature.^{9,14}

Measurements in the Vascular Laboratory

The patient's visit to the VL took place within two weeks after his (last) visit to the GPC. The tests in the VL were performed by (two) experienced vascular laboratory technicians using sophisticated ultrasound instruments (Medasonics Vasculab D10 (8 MHz) and Medasonics Vasculab Spectrum Analyzer SP25). The VL technician had no prior knowledge of either the results of the GPC measurement or the clinical condition of the patient. Measurements were performed on the right arm and on both ankles at rest and after a standardized walking test on a treadmill. The VL technician also interpreted the acoustic and audiospectrum analyzed pulse-wave-signals from the posterior tibial and dorsalis pedis arteries as being either 'normal' or 'pathologic'. After the last patient had visited the VL, both VL technicians independently reviewed all VL registration forms to categorize legs as to whether PAOD was present or not. Subsequently, they sought consensus on those cases they disagreed upon. Criteria for a positive VL diagnosis were: a resting AB-ratio lower than 0.90, a significant drop in the AB-ratio after exercise (below 0.90) and pathologic waveforms over both pedal arteries.

Analysis

Since single Doppler measurements could not be obtained in three legs, data on 116 left legs and 115 right legs of 117 patients were suitable for analysis. In the subgroup of patients of whom also repeated measurements were available, data on 47 left legs and 45 right legs of 51 patients were included in the analysis.

From a 2x2 table, comparing the diagnostic outcome of the GPCs with the diagnostic conclusion of the VL, accuracy (percentage correct classifications), sensitivity, specificity, likelihood ratios (LR+, LR-) and the diagnostic odds ratio (OR) were calculated.⁴⁰ Data from left and right legs were combined. Confidence intervals (95%) were calculated for left and right legs separately and then averaged.^{41,42}

A Receiver Operating Characteristic (ROC) analysis was done to describe the association between sensitivity and specificity at different cutoff values and to estimate the theoretical optimum cutoff value. This is the AB-ratio with the highest sum of sensitivity and specificity.^{43,44} Using logistic regression, smoothed ROC curves were designed as well ('model'). ROC analyses were also performed for males and females separately and the smoothed ROC curves were used to compare the sexes with respect to maximum validity and optimum cutoff value (*appendix chapter 8*). A method was used that allowed for the dependence of left and right legs of each patient.⁴⁵⁻⁴⁷

On the basis of the figures for sensitivity and specificity threshold cutoff values of the AB-ratio were calculated for a PV+ $\geq 95\%$ and a PV- $\geq 99\%$ at three different levels of prior probability of PAOD (33%, 10%, 5%), following Bayes' theorem. This range of prevalence figures was reasonable for the 'indicated population' in general practice.^{29,30,33,34,48,49}

Results

Population

Table 8.1 displays the prevalence of leg problems in the study population according to the GPC patient records. According to the questionnaire, eight percent of all patients currently had complaints of IC. According to the VL criteria PAOD was present in 33% of all legs (42% of all patients). Only seven (VL) to eight percent (GPCs) of all legs had a resting AB-ratio lower than 0.70, which is considered to indicate 'major disease'.²⁹ *Table 8.2* presents the distribution of the resting AB-ratios measured in the GPCs. The range of overlap of AB-ratios of diseased and non-diseased legs was smaller if the mean of three consecutive AB-ratios was taken for test outcome.

Diagnostic value and accuracy at the preset cutoff value of 0.95

The comparison between GPC outcome and VL outcome, using the preset cutoff value of 0.95 resulted in the following diagnostic parameters (between brackets the 95% ci). When the AB-ratio was measured once, sensitivity was 71% (54-85%), specificity 83% (73-91%), LR+ 4.2 (2.5-7.6), LR- 0.35 (0.21-0.58) and the diagnostic odds ratio (OR) was 12 (5-31). If the mean of three consecutive AB-ratios was taken for test-outcome, sensitivity was 91% (72-99%), specificity 83% (61-95%), LR+ 5.3 (2-15), LR- 0.11 (0.03-0.4) and the OR was 50 (8-318). In spite of the large confidence interval, the diagnostic odds ratio was much higher in the subgroup with

Table 8.1 Leg problems in the study population according to the GPC patient records

Diagnosis	Number of patients
<i>No leg problems</i>	54
<i>Intermittent claudication and/or vascular surgery or PTA^a</i>	22
- without other leg problems	13
- with other leg problems	
- osteoarthritis	4
- varicose veins	2
- peripheral neuropathy	2
- other complaints	1
<i>Other leg problems, no PAOD</i>	41 ^b
- osteoarthritis	21
- varicose veins	10
- peripheral neuropathy	9
- other complaints	8
Total	117

^a percutaneous transluminal angioplasty^b some patients with more than one leg problem**Table 8.2** Distribution of the general practice centre AB-ratio according to vascular laboratory disease status

VL outcome	General practice centre AB-ratio	
	<i>One measurement</i> (231 legs; PAOD+: 76 legs)	<i>Mean of three measurements</i> (92 legs; PAOD+: 46 legs)
PAOD +	range 0.44-1.10 mean 0.82	0.52-1.01 0.78
PAOD -	range 0.75-1.36 mean 1.06	0.88-1.23 1.05

VL: vascular laboratory

repeated measurements than in the single measurement group: 50 versus 12 respectively.

In case of a single AB-ratio measurement the accuracy of the GPC outcome was 79%. False negative classifications (FN) occurred in 22 legs of 18 patients (9.5% of all legs). There were false positive classifications (FP) in 26 legs of 21 patients (11.3% of all legs). Taking the mean of three consecutive AB-ratios for test outcome and correcting for the higher prevalence in this subgroup, accuracy was 85%, the percen-

tage of FN decreased to 3.0% and the percentage of FP increased slightly to 11.7% of all legs.

ROC analyses

ROC analyses for males and females separately revealed no significant differences between the sexes with respect to maximum validity and optimum cutoff value. *Table 8.3* and *figure 8.1* show the results of the ROC analyses for the population as a whole. The ROC curve representing the repeated measurements is positioned more towards the upper left corner of the figure than the curve representing the single measurements. This implies that one should always perform repeated measurements before reaching a definite diagnostic conclusion.

In case of a single AB-ratio measurement the ROC analysis yielded 0.97 (95% ci: 0.86-1.04; model: 0.89-1.05) as theoretical optimum cutoff value. The associated diagnostic parameters were (95% ci between brackets): sensitivity 79% (63-90%), specificity 82% (72-90%), LR+ 4.4 (2.7-7.6), LR- 0.26 (0.14-0.48), OR 17 (7-55). Accuracy was 81%.

If the mean of three consecutive AB-ratio measurements was taken for test outcome, the ROC analysis yielded 0.92 (95% ci: 0.82-1.02; model: 0.90-0.95) as theoretical optimum cutoff value. Now the associated diagnostic parameters were: sensitivity 87% (67-97%), specificity 91% (72-99%), LR+ 10 (2.6-73), LR- 0.14 (0.05-0.41), OR 70 (11-688). Accuracy, corrected for prevalence, was 90%.

Threshold cutoff values

Table 8.4 shows the threshold cutoff values of the AB-ratio calculated for a desired value for PV+ of 95%, a desired value for PV- of 99% and prevalence figures in the range 5-33%.

Discussion

In this study the performance of the AB-ratio as a tool for diagnosing PAOD in general practice was assessed. In theory the ideal study population would have been the 'indicated population', i.e. patients who visit their general practitioner and of whom the clinical picture (medical history, physical examination) motivates the general practitioner to perform a Doppler measurement.^{9,14} This would have required a long period of data collection or a large number of participating general practitioners and more than one cooperating vascular laboratory. For reasons of efficiency we selected the study population from a cohort of the Limburg PAOD Study. The spectrum of PAOD and co-morbidity in this population appeared appropriate for assessing the validity of the AB-ratio in a non-specialist setting: relatively mild disease predominated and sufficient non-arterial leg complaints were present as well.

For practical reasons we could not perform repeated measurements in all patients.^{39,50} Instead we used available data of a subgroup of patients who had visited their GPC three times during the last eight months as part of the Limburg PAOD Study. This was allowed because we only included legs with a stable pattern of consecutive AB-ratios. When extrapolating the results of this subgroup to the total study population (accuracy, FN, FP) we corrected for the higher prevalence of PAOD in this subgroup, according to Bayes' theorem.

Figure 8.1 ROC curves of the general practice centre AB-ratio

— empirical data - - - model *a* single measurement *b* mean of 3 measurements

Table 8.3 ROC analyses. Sensitivity and specificity of the GPC resting AB-ratio at different cutoff values for single and repeated measurements (between brackets the values for the 'smoothed' models)

Cutoff value	Single GPC measurement (n = 231 legs)		Mean of 3 GPC measurements (n = 92 legs)	
	<i>Sensitivity</i> [*]	<i>Specificity</i> [*]	<i>Sensitivity</i> [*]	<i>Specificity</i> [*]
1.15	100 (100)	19 (19)	100 (100)	22 (22)
1.10	100 (99)	37 (36)	100 (100)	30 (30)
1.05	92 (93)	56 (56)	100 (100)	50 (50)
1.00	83 (86)	76 (70)	98 (98)	72 (72)
0.95	71 (73)	83 (84)	93 (95)	80 (82)
0.90	67 (67)	89 (88)	83 (85)	91 (93)
0.85	53 (55)	94 (95)	70 (68)	100 (99)
0.80	43 (44)	98 (98)	50 (50)	100 (100)
0.75	33 (35)	99 (100)	39 (39)	100 (100)
0.70	24 (26)	100 (100)	26 (26)	100 (100)

^{*} rounded figures

Table 8.4 'Threshold' cutoff values of the AB-ratio for PV+ $\geq$ 95% and PV- $\geq$ 99% at different levels of prior probability

Prior probability	Cutoff value below which PV+ $\geq$ 95%		Cutoff value above which PV- $\geq$ 99%	
	Single measurement	Mean of 3 measurements	Single measurement	Mean of 3 measurements
33% (this study)	< 0.79	< 0.88	> 1.09	> 0.98
10%	< 0.75	< 0.88	> 1.07	> 0.94
5%	< 0.75	< 0.88	> 1.02	> 0.88

The 'gold standard' in this study was the consensus diagnosis made by two experienced VL technicians on the basis of the results of a combination of noninvasive tests. Duplex scanning was not used and segmental pressure measurements or wave form analysis of proximal leg arteries were not performed. With those techniques the exact site of an arterial obstruction or stenosis can be established, which was not our aim. Furthermore, duplex scanning is not the primary diagnostic procedure to establish or exclude the diagnosis 'PAOD', but is used before percutaneous transluminal angioplasty or vascular surgery.

The ROC analyses (*table 8.3, figure 8.1*) demonstrated that performing repeated measurements is always better than performing a single measurement. Using a cutoff value for the pocket Doppler AB-ratio of 0.95, yielded acceptable results for accuracy and diagnostic parameters especially in the repeated measurement situation. The better performance of the Doppler method in case of repeated measurements was mainly achieved through a reduction in false negative test results.

The ROC analyses yielded theoretical optimum cutoff values (single measurement: 0.97; mean of three measurements: 0.92) that did not differ much from the preset cutoff value (0.95) used in the GPCs. *Hiatt et al.*, using a different approach, reported to consider an AB-ratio at rest < 0.94 to be abnormal.⁸ In our study the Doppler method performs best when a cutoff value of 0.92 for the mean of three consecutive AB-ratio measurements is used (sensitivity 87%, specificity 91%, LR+ 10, LR- 0.14).

At the theoretical optimum cutoff value sensitivity and specificity are given about equal weight.⁴⁴ If a higher sensitivity (less FN) or a higher specificity (less FP) is preferred, a different cutoff value should be chosen. Our results (*table 8.3, figure 8.1*) may help an investigator to decide whether to accept the qualities of the resting AB-ratio at each cutoff value, or to use an alternative procedure.⁵¹⁻⁵⁴

In everyday practice the positive and negative predictive value of the measured AB-ratio are more relevant than a fixed cutoff value. Often it is relevant to rule out disease. A false negative Doppler result implies that therapy which is in fact appropriate will not be started or that referral to a specialist will be postponed. To rule out disease (high PV-) in a population with a relatively low prevalence, a cutoff value with a high sensitivity — i.e. higher than the theoretical optimum cutoff value — has to be chosen.⁴⁰

On the other hand, establishing a diagnosis is important as well. A false positive

Table 8.5 Decision rules for the measurement and interpretation of the pocket Doppler AB-ratio (in the range of prior probabilities of 5-33%; based on table 8.4)

AB-ratio	Action	Interpretation
AB-ratio > 1.09	even if single measurement:	no PAOD (99% certain)
AB-ratio 0.75-1.09	repeat measurement (e.g. 2 more times): - if mean AB-ratio > 0.98: - if mean AB-ratio < 0.88: - if mean AB-ratio 0.88-0.98:	no PAOD (99% certain) PAOD (95% certain) the higher the prior probability that PAOD is present the higher the AB-ratio has to be to rule out disease ^a
AB-ratio < 0.75	even if single measurement:	PAOD (95% certain)

^a e.g. if prevalence is 5% then the AB-ratio has to be > 0.88 and if prevalence is 10%, then the AB-ratio has to be > 0.94 to rule out PAOD

conclusion implies that a patient is labelled 'PAOD' incorrectly and thus will receive the advice to 'stop smoking and keep walking' on an erroneous basis.⁵⁵ Although this advice would be beneficial to many patients, being labelled 'PAOD' could lead to fear of disablement or limb loss. Furthermore, referral to a specialist or vascular laboratory should be as efficient as possible. To establish a diagnosis (high PV+) in a population with a relatively low prevalence a cutoff value for the AB-ratio associated with a high specificity should be selected.⁴⁰ Then, a cutoff value lower than the theoretical optimum has to be chosen.

On the basis of our threshold cutoff values of the AB-ratio for high predictive values (table 8.4) practical decision rules for the use and interpretation of the Doppler method can be derived for the range of prior probabilities of 5-33% (table 8.5). By repeating the Doppler measurement, the range of less conclusive AB-ratios is reduced from 0.75-1.09 to 0.88-0.98. Within this range it applies that the higher the prior probability of PAOD, the higher the AB-ratio should be to rule out disease. The prior probability of PAOD in this diagnostic situation depends not only on age and gender of the patient but also on the results of history and physical examination performed by the doctor.

We conclude that the measurement of the AB-ratio with a hand-held Doppler device is a valid diagnostic method for general practice. To maximize diagnostic performance one ought to measure the AB-ratio on more than one occasion before reaching a definite diagnostic conclusion. In that case the Doppler method can be a useful tool to support diagnostic decision making in daily practice.

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Chapter 9 The prevalence of symptomatic and asymptomatic peripheral arterial occlusive disease. The Limburg PAOD Study.*

Summary *The prevalence of peripheral arterial occlusive disease (PAOD), including asymptomatic cases and cases unknown to the general practitioner, was estimated in 18884 patients, aged 45-75 years, on the list of 18 general practice centres (GPCs).*

The study population (n=3171) consisted of a sample of the total population. In the GPCs data were collected on intermittent claudication (IC), peripheral pulses, vascular risk factors, cardio- and cerebrovascular disease and the ankle brachial systolic pressure ratio (AB-ratio). PAOD was defined as an AB-ratio < 0.95 on two consecutive occasions. Results were recalculated for the total population.

The prevalence of PAOD was 6.9% (95%ci 5.7-8.2%). One third (2.2%) of all cases had an AB-ratio < 0.75. The prevalence of IC was 6.6% (95%ci 5.2-7.9%), of which a quarter (1.6%) met the classic WHO-criteria. The prevalence of abnormal pedal pulses was 8% (95%ci 6.5-9.5%). PAOD did not occur significantly more often among men than among women but men suffered more often from an advanced stage of PAOD. Of all cases of PAOD 22% was symptomatic. This proportion correlated positively with higher age, male gender and lower AB-ratio. Among asymptomatic PAOD cases the prevalence of concomitant cardio- and cerebrovascular disease was three to four times as high as in the group without PAOD. Sixty-eight % of all PAOD cases was unknown to the general practitioner. This 'unknown' group mainly represented less advanced cases of atherosclerosis. However, in the group of PAOD cases with an AB-ratio < 0.75, 42% was unknown to the general practitioner.

We conclude that general practitioners succeed in selecting the worst cases of manifest atherosclerosis but can enhance their efforts towards secondary prevention.

Key words *peripheral arterial occlusive disease, epidemiology, population study, general practice, prevalence, intermittent claudication, noninvasive testing*

Introduction

Peripheral arterial occlusive disease (PAOD) is one of the many terms to describe the manifestation of atherosclerosis below the bifurcation of the abdominal aorta. Due to ageing of the population in western societies, the prevalence of atherosclerotic disease will rise and the diagnostic and therapeutic management (adequate

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diagnosis, regular follow up, conservative therapy, preventive measures and selection for referral) of this chronic disease will become more important to general practitioners.¹⁻⁴

Figures on the prevalence of PAOD diverge, depending on study population and diagnostic criteria. In general practice morbidity registrations, patients with intermittent claudication who visited their general practitioner are included.⁵⁻⁷ Such figures depict the work load a chronic disease entails to primary health care. They also indicate the 'prior probability' of PAOD, which is important in the diagnostic process of the general practitioner. Data from population studies demonstrate the total extent of the burden this disease could impose on the health care system. In many studies the WHO-questionnaire on intermittent claudication was used (symptomatic cases of PAOD).⁸⁻¹⁵ In a number of population studies also noninvasive diagnostic techniques were applied.¹⁶⁻²² In the latter studies both symptomatic and asymptomatic cases were observed.

A review of these studies suggests that only a minority of all PAOD patients is known as such in primary health care ('tip of the iceberg').^{2,23} It is unclear whether the unknown cases of PAOD represent a subcategory of patients with atherosclerosis to whom the general practitioner should pay more attention, either for therapeutic or preventive reasons.

Moreover, there appears to be a large group of 'asymptomatic' or 'atypical' patients with PAOD.^{2,23} The importance of asymptomatic PAOD was recently demonstrated by the results of a longitudinal study showing that not only symptomatic patients, but also asymptomatic patients had a higher cardiovascular mortality as compared to subjects without PAOD.²⁴

Review of the literature also brought up the question whether the general idea of PAOD as a predominantly male disease is correct.

The aim of the present study was to estimate the prevalence of PAOD in a population of middle-aged and elderly men and women. We were especially interested in the proportion of asymptomatic disease and in the number of PAOD cases 'unknown' to the general practitioner. We also investigated the association of PAOD with cardio- and cerebrovascular disease.

Method

Background

The 'Limburg PAOD Study' is a research project conducted by the University of Limburg in Maastricht (the Netherlands) and a number of general practice centres in the region. This project consists of three interrelated elements: a prevalence study, a diagnostic study and an intervention study (on aspirin).^{3,25} The results of the prevalence study are presented here.

General design

In the Netherlands every subject is registered in a general practice. Therefore, the registered population of a general practice is a segment of the general population. From the list of eighteen general practice centres all patients were identified who were between 40 and 75 years of age (*source population*). For reasons of efficiency data were collected in a part of this population, selected through a stratified sampling procedure (*study population*). Strata were formed by gender, age category

and the score on a postal questionnaire that had been sent to all patients of the source population. Prevalence figures for the general population were recalculated from the stratum specific data yielded by the study population to the population of patients who had responded to the postal questionnaire (*base population*).

Sampling procedure

All patients on the list of the 18 general practice centres, who were between 40 and 75 years of age, received a postal questionnaire with 5 yes/no questions: pain on walking, smoking ≥ 15 cigarettes, known high blood pressure, diabetes, heart disease or TIA/stroke. Thus, each responder was characterized by a 'prior risk score' between 0 and 5. The population invited to participate in the study was composed of three categories. A random sample was drawn from the category with risk score 0. Another random sample was drawn from the population with risk score 1-5. Subsequently, from the remaining patients in the latter category, those with the highest risk score were selected (score 5, 4, 3 and in some practices score 2). This complex sampling procedure was necessary to meet the demands of the three studies mentioned above in an efficient way.

Data collection

Each participant filled in a *questionnaire* which incorporated the WHO-questionnaire on intermittent claudication.⁸ The questionnaire also contained questions on smoking habits. The general practitioner subsequently performed a *physical examination* (palpation of the pedal and femoral pulses, auscultation of the femoral artery). He also copied relevant data from the *patient record* to the registration form (presence of peripheral, cardio- or cerebrovascular disease, hypertension, hypercholesterolaemia, diabetes mellitus).

Without knowing the results of the general practitioner's examination, the practice assistant (or a colleague general practitioner) assessed the *ankle brachial systolic pressure ratio (AB-ratio)* of both legs using a hand-held Doppler device (Huntleigh Mini Dopplex D500, 8MHz) and a mercury sphygmomanometer.^{1,26} Systolic pressures were recorded on both arms and legs with the patient lying in supine position. The AB-ratio was defined as the systolic pressure at the ankle divided by the highest systolic arm pressure. If the AB-ratio of at least one leg was less than 0.95, the patient was requested to return for a second assessment one week later. All sphygmomanometers were calibrated before the start of the study. The general practitioners and practice assistants had been trained in performing AB-ratio measurements. In a previous study the reproducibility of these measurements proved to be satisfactory.²⁷

Definitions

The general practitioner indicated whether a patient was already known to him as suffering from PAOD ('PAOD according to patient record') and whether such a patient had experienced percutaneous transluminal angioplasty (PTA), vascular surgery or an amputation ('specialist care'). If the patient record mentioned the diagnoses angina pectoris, coronary ischemia or myocardial infarction the patient was considered to suffer from *ischemic heart disease (IHD)*. If the patient record mentioned carotid stenosis, TIA, RIND or stroke, the patient was considered to suffer from *cerebral arterial disease (CeAD)*.

The variable '*intermittent claudication*' (IC) was divided in two main categories: definite IC and non-calf IC. The category '*definite IC*' was defined according to the criteria developed by Leng and co-workers: pain or discomfort in the calf when walking (at an ordinary pace on the level or uphill or when in a hurry), never beginning when standing still or sitting.^{28,29} This category comprised 2 subcategories. Firstly, the subcategory '*Rose*' was defined as: definite IC, restricted to 'pain' (excluding other complaints), also meeting two extra criteria: 'not disappearing while walking' and 'stopping or slow down when you get it'.⁸ Secondly, the subcategory '*pain or discomfort, not meeting all Rose-criteria*' was defined as: definite IC (pain or other complaints), not meeting the two extra criteria. The category '*only non-calf IC*' was defined as absence of definite IC, but presence of non-radiating pain or discomfort in buttock, thigh or foot, and otherwise meeting the overall criteria for definite IC.

The *pedal pulses* (dorsalis pedis artery and tibial posterior artery) were called 'abnormal' if the following combinations of pulses occurred: both pulses absent, or both pulses weak, or one pulse absent and the other one weak. Other positive test results were absence of the *femoral artery pulse* and presence of a *femoral bruit*.

After the physical examination the general practitioner had to state whether he thought PAOD (i.e. intermittent claudication) was currently present ('GP's *diagnosis*').

PAOD was considered to be present in a leg, if the AB-ratio was lower than 0.95 on two consecutive occasions. This cutoff value was a balanced choice between the 'specific' cutoff value of 0.90 (sensitivity 75-100%, specificity 80-100%) and the 'sensitive' cutoff value of 1.0 (sensitivity 88-100%, specificity 60-81%) as reported in studies on the validity of the Doppler-method.³⁰⁻³⁵ This relatively high cutoff value was chosen because in primary care a sensitive cutoff value is more important than in the specialist's setting, where a high specificity (i.e. a lower cutoff value) is desired.

Some analyses also were carried out at lower cutoff values of the AB-ratio: 0.75 and 0.50. Below 0.75 a stenosis or occlusion is definitely present and referral to a vascular specialist might be useful, e.g. to answer the question whether PTA is appropriate. Values for the AB-ratio smaller than 0.50 indicate that multiple occlusions are probable and surgical intervention might be considered.¹

PAOD was called '*symptomatic*' if the AB-ratio was lower than 0.95 and there were leg complaints meeting the criteria for intermittent claudication (definite and non-calf). '*Asymptomatic*' PAOD was defined as the combination of an AB-ratio lower than 0.95 with no symptoms of intermittent claudication. A case of PAOD was called '*known*' if the AB-ratio was lower than 0.95 and there was PAOD according to the patient record.

Analysis

Due to the time period that passed between postal questionnaire and general practitioner's examination, the youngest (40-45 years) and oldest age category (>75 years) were incomplete. These age categories were excluded from the analysis.

The study population and base population were divided in strata defined by the variables 'age' (45-55, 55-65, 65-75), 'gender' (male, female) and 'prior risk score' (0-5). Prevalence figures for the base population were recalculated as appropriately weighted means of stratum-specific prevalences. Confidence intervals (95%) were

Table 9.1 Prevalence of atherosclerotic disease as registered by general practitioners (n=18884, 47.2% men; age 45-75 years, mean age 58.6 years)

Atherosclerotic disease	Prevalence (95% ci) %		Prevalence by gender (95% ci) %	M/F ratio
PAOD according to patient record*	3.8 (2.9-4.6)	M	5.9 (4.2- 7.6)	2.8
		F	2.1 (1.3- 2.9)	
- of whom had experienced 'specialist care'	1.6 (1.0-2.2)	M	3.0 (1.6- 4.5)	5.8
		F	0.5 (0.1- 0.9)	
Ischemic heart disease (IHD)*	10.8 (9.5-12.1)	M	15.6 (13.0-18.1)	2.3
		F	6.9 (5.6- 8.2)	
Cerebral arterial disease (CeAD)*	3.4 (2.4-4.4)	M	5.2 (3.2- 7.3)	2.6
		F	2.0 (1.0- 2.9)	

* definitions: see text

based on normal approximation and p-values for differences in prevalence figures were calculated using an unpaired two-sample t-test.

Results

Populations

The *source population* consisted of 26620 patients (male: 47.5%) with a mean age of 56.5 years (SD: 9.8 years). The number of patients that returned the postal questionnaire was 23004 (86.4%). The distribution of age and gender in the population of responders was the same as in the source population.

As result of the sampling procedure 5301 patients were invited to partake in the study. The participation rate was 68.9%. *Non-participation* was due to various reasons: patients had died, had moved, or were absent due to protracted admission to a hospital or nursing-home (17.5% of the non-participants); patients showed 'no interest' (48%); there were medical or practical reasons according to the general practitioner (11%). For a quarter of the non-participation the reason remained unknown.

The *study population* consisted of 3654 patients aged 40.7-78.3 years (mean: 59.1 years). Data analysis was restricted to 3171 patients (male: 47.2%) who were between 45 and 75 years of age (mean: 59.8 years, SD 8.0 years). Frequencies found in this population were used to calculate the prevalence figures for the *base population*, which consisted of 18884 patients (male: 47.3%) between 45 and 75 years (mean: 58.6 years, SD 8.1 years).

Registered atherosclerotic morbidity

Table 9.1 presents the recalculated prevalence in the base population of various manifestations of atherosclerotic disease as registered in the patient records of the general practitioners. Among men the prevalence of registered atherosclerotic morbidity is significantly higher than among women. The proportion of cases of PAOD according to the patient record, who had experienced PTA, vascular surgery or an amputation is 52% among men and 25% among women.

Table 9.2 Prevalence of clinical signs and symptoms associated with PAOD (n=18884, 47.2% men; age 45-75 years, mean age 58.6 years)

Signs and symptoms (definitions: see text)	Prevalence (%), total (95% ci)	Male/ Female- ratio
IC, questionnaire, all	6.6 (5.2-7.9)	1.2
- definite (calf)	5.3 (4.2-6.5)	1.3
<i>· meeting Rose-criteria</i>	1.6 (0.9-2.2)	0.6
<i>· pain or discomfort, not meeting Rose-criteria</i>	3.7 (2.7-4.7)	1.8
- only non-calf	1.2 (0.6-1.9)	0.7
Abnormal pedal pulses	8.0 (6.5-9.5)	0.8
Absent femoral pulse	1.0 (0.5-1.5)	0.5
Femoral bruit	4.5 (3.6-5.9)	1.4
<i>GP's diagnosis</i>	2.7 (2.0-3.3)	3.0

Current signs and symptoms of PAOD

Table 9.2 shows the prevalence figures of clinical signs and symptoms associated with PAOD, as recalculated based on the population survey. The prevalences of IC, abnormal pedal pulses and a femoral bruit increase with rising age. Women more often meet the Rose-criteria for IC than men. The figures on clinical signs and symptoms do not demonstrate an unequivocal male predominance. Nonetheless, general practitioners diagnose 'PAOD' more often among men than among women. This difference is significant in the two oldest age categories.

Noninvasive testing

The mean AB-ratio in the base population is 1.08 (men:1.10, women 1.07). Seven percent of the base population has an AB-ratio of 0.95 or less. In only 0.4% (95% ci 0.1-0.6) an AB-ratio of 0.50 or less is present. Figure 9.1 presents the cumulative frequency distribution of the AB-ratio for the range of 'positive' Doppler outcomes (i.e. AB-ratios lower than 0.95). The frequency of a positive Doppler outcome is higher for men as compared to women at each cutoff value of the AB-ratio. This difference is significant for the range of AB-ratios between 0.65 and 0.85. The total prevalence of PAOD (twice an AB-ratio < 0.95) among women (6.5%; 95% ci: 4.8-8.2) is not significantly lower than the prevalence in men (7.2%; 95% ci: 5.5-9.0).

Table 9.3 provides the prevalence figures of PAOD for the various age and gender

	Prevalence in % (95% ci) 45-55 years (<i>m</i> =3474, <i>f</i> =3590)	55-65 years (<i>m</i> =3381, <i>f</i> =3735)	65-75 years (<i>m</i> =2071, <i>f</i> =2633)
M	3.7 (1.0-6.4)	9.2 (5.5-12.8)*	10.1 (5.7-14.6)
F	5.7 (2.4-9.1)	4.9 (2.6-7.3)	8.2 (4.3-12.1)
M	2.8 (0.4-5.3)	8.4 (4.7-12.0)*	8.8 (4.4-13.2)
F	2.8 (0.7-4.9)	4.6 (2.3-6.9)	7.5 (3.6-11.4)
M	0.5 (0.2-0.9)	0.9 (0.5-1.3)	2.4 (1.5-3.3)
F	0.3 (0.1-0.5)	2.2 (0.4-4.1)	3.7 (0.3-7.0)
M	2.3 (0-4.7)	7.5 (3.9-11.1)*	6.4 (2.1-10.8)
F	2.5 (0.4-4.6)	2.3 (0.9-3.7)	3.8 (1.6-5.9)
M	0.9 (0-2.0)	0.8 (0.4-1.2)	1.3 (0.6-2.0)
F	2.9 (0.3-5.6)	0.4 (0.1-0.7)	0.7 (0.2-1.2)
M	2.7 (0.2-5.1)	6.6 (3.8-9.4)	17.6 (11.3-23.8)
F	5.6 (2.6-8.6)	8.3 (4.9-11.6)	13.8 (8.4-19.2)
M	0.2 (0-0.5)	0.3 (0.1-0.6)	2.1 (0-4.7)
F	1.8 (0-3.5)	1.3 (0.2-2.3)	0.8 (0.3-1.3)
M	2.0 (0.8-3.3)	6.2 (3.2-9.2)	9.5 (5.3-13.7)
F	2.2 (0.4-4.0)	4.3 (1.9-6.8)	6.8 (2.6-11.1)
M	1.4 (0.2-2.6)	3.7 (1.8-5.6)*	10.6 (5.6-15.5)*
F	0.8 (0-1.9)	1.0 (0.6-1.4)	2.9 (2.0-3.7)

* $p < 0.05$ for differences between men and women in the same age category (unpaired two sample t-test)

categories. The prevalence of PAOD increases with rising age. In the youngest age group the prevalence among women is higher, in the oldest age category the prevalence among men is higher. These differences are not statistically significant. However, the figures on symptomatic cases, cases with concomitant IHD or CeAD and known cases, indicate that the proportion of cases with manifest atherosclerosis is evidently higher among men.

Table 9.4 shows that the proportions of symptomatic cases, cases with concomitant IHD or CeAD and known cases, are larger at the cutoff value of 0.75. The prevalence of PAOD is higher in patients with a diagnosis of hypertension, hypercholesterolaemia or diabetes mellitus in their patient record. Smoking, currently or in the past, also increases the probability of PAOD being present (table 9.5).

Symptomatic and asymptomatic PAOD

Twenty-two percent of all PAOD cases is symptomatic. Of these symptomatic cases 75% is male, 49% belongs to the oldest age group, 69% has an AB-ratio lower than 0.75, 12% has an AB-ratio lower than 0.50. The proportion having concomitant IHD is 33%, CeAD 6%.

On the other hand, of the asymptomatic cases only 43% is male, 22% has an AB-ratio lower than 0.75 and 2% has an AB-ratio lower than 0.50. The age distribution is shifted only slightly to the younger age groups (oldest age group 47%) as com-

Table 9.3 Prevalence of PAOD according to noninvasive testing (n=18884, 47.2% men; age 45-75 years, mean age 58.6 years)

Category	Prevalence in % (95% ci)	Male/ Female ratio
PAOD, total (2x AB-ratio < 0.95)	6.9 (5.7-8.2)	1.1
symptomatic cases (IC present)	1.5 (1.1-1.9)	3.3
concomitant IHD or CeAD	2.4 (1.9-3.0)	2.6
known cases	2.2 (1.6-2.8)	2.5

Figure 9.1 Number of patients with an AB-ratio lower than a specific cutoff value. Cumulative frequency (y-axis) for the range of cutoff values of the AB-ratio in the range between 0.50 and 0.95 (x-axis) (n=18884, 47.2% men; age 45-75 years, mean age 58.6 years)

pared to the symptomatic cases. The proportion having concomitant atherosclerosis also does not differ much from the symptomatic cases (IHD 29%, CeAD 12%).

	Prevalence in % (95% ci)		
	45-55 years (m=3474, f=3590)	55-65 years (m=3381, f=3735)	65-75 years (m=2071, f=2633)
M	1.6 (1.0 - 2.1)	7.7 (4.9 - 10.6)	16.4 (10.6 - 22.3)
F	3.1 (1.0 - 5.2)	6.8 (3.8 - 9.7)	11.2 (7.0 - 15.3)
M	0.5 (0.1 - 0.8)	3.1 (1.3 - 5.0)*	4.8 (2.0 - 7.5)*
F	0.3 (0 - 0.5)	0.6 (0.2 - 0.9)	1.7 (1.0 - 2.4)
M	0.6 (0.3 - 1.0)*	3.4 (1.9 - 4.8)*	8.9 (4.9 - 13.0)*
F	0.1 (0 - 0.3)	1.6 (0.6 - 2.7)	3.0 (1.4 - 4.7)
M	0.7 (0.3 - 1.1)	2.8 (1.4 - 4.2)*	8.7 (4.0 - 13.4)*
F	0.7 (0 - 1.7)	0.9 (0.5 - 1.3)	2.9 (1.3 - 4.5)

* $p < 0.05$ for differences between men and women in the same age category (unpaired two sample t-test)

Table 9.4 Characteristics of PAOD at 2 cutoff values* for the AB-ratio (n=18884, 47.2% men; age 45-75 years, mean age 58.6 years)

Gender	Cut off value AB- ratio	Prevalence in % (95% ci)	Proportion 'symptomatic'	concomitant IHD/CeAD	'known'
Men	0.75	3.4 (2.2-4.6)	53%	57%	58%
	0.95	7.2 (5.5-9.0)	34%	50%	46%
Women	0.75	1.3 (0.8-1.8)	32%	46%	57%
	0.95	6.5 (4.8-8.2)	11%	22%	20%
All	0.75	2.2 (1.7-2.8)	47%	54%	58%
	0.95	6.9 (5.7-8.2)	22%	35%	32%

* due to sparse data in the study population for the age categories 45-55 years and 55-65 years, the results for an AB-ratio < 0.50 are not presented

PAOD and concomitant arterial disease

The total prevalence of ischemic heart disease in the base population is 10.8% (table 9.1). If PAOD is present (AB-ratio < 0.95) the probability of IHD increases to 29.6%. In the subcategory of PAOD patients with an AB-ratio lower than 0.75, the prevalence of IHD is 49.6%. If PAOD is absent (AB-ratio $\geq$ 0.95) the probability of IHD is 9.3%. The total prevalence of cerebral arterial disease is 3.4% (table 9.1). If PAOD is present the probability of CeAD increases to 11.0%. In the subcategory of PAOD patients with an AB-ratio lower than 0.75, the prevalence of CeAD is 13.1%. If PAOD is absent the probability of CeAD is 2.8%.

Reversely, the prevalence of (symptomatic and asymptomatic) PAOD is 19.1 % among patients with IHD and 22.5% among patients with CeAD. If IHD or CeAD are absent these figures are 5.4% and 6.3% respectively.

Table 9.5 Prevalence of PAOD in various vascular risk groups (n=18884, 47.2% men; age 45-75 years, mean age 58.6 years; prevalence of PAOD 6.9%)

Vascular risk indicator	Status	(prevalence in %; 95% ci)	Probability of PAOD in %	Relative Risk*
Hypertension	present	(24.2; 22.0 - 26.4)	13.3	2.8
	absent		4.8	1
Hypercholesterolaemia	present	(8.7; 7.1 - 10.3)	12.4	2.0
	absent		6.2	1
Diabetes mellitus	present	(5.6; 4.6 - 6.7)	20.5	3.3
	absent		6.2	1
Smoking	ever smoked	(65.4; 62.3 - 68.4)	8.0	1.7
	- smoking	(36.7; 33.8 - 39.5)	8.7	1.8
	- stopped	(28.7; 25.8 - 31.6)	7.2	1.5
	never smoked		4.8	1

* bivariate RR

Known and unknown cases of PAOD

Thirty-two per cent of all cases of PAOD (AB-ratio < 0.95) is known as such to their general practitioner; in general this proportion is larger when the AB-ratio is lower (*tables 9.3 and 9.4*). Of these known cases 69% is male, 60% is older than 65 years and 60% has concomitant cardio- or cerebrovascular disease. Thirty-seven per cent of the known cases has complaints of intermittent claudication (symptomatic PAOD). The proportion of known cases with an AB-ratio of 0.75 or less is 59%, while an AB-ratio of 0.50 or less occurs in 5% of known cases.

Of the unknown PAOD cases 60% is female, 58% is younger than 65 years, only 24% has concomitant cardio- or cerebrovascular disease and only 15% is symptomatic. The proportion of unknown cases with an AB-ratio of 0.75 or less is 20% and an AB-ratio of 0.50 or less occurs in 4% of the unknown PAOD cases.

The probability that a patient with PAOD is known as such to his general practitioner is higher when he has complaints of IC (53% of the symptomatic cases is known against 26% of the asymptomatic cases), also suffers from other atherosclerotic disease (53% of the cases with concomitant IHD or CeAD is known against 20% of cases without concomitant manifestations of atherosclerosis) and is older than 65 (40% of the cases who are 65-75 years of age are known against 28% in the age group 45-55 and 24% in the age group 55-65). The proportion of known cases of PAOD among men is higher than among women (*table 9.4*).

Discussion

In this population study the prevalence of PAOD (twice an AB-ratio lower than 0.95) in the age group of 45-75 years, was 6.9% of which one third (2.2%) had an AB-ratio lower than 0.75. The prevalence of current complaints of intermittent claudication was 6.6%, of which a quarter (1.6%) met the WHO/Rose-criteria.⁸ The prevalence of PAOD according to the patient record of the general practitioners was lower (3.8%).

Signs and symptoms

There is no consensus on the 'correct' definition of IC. Our definition permits comparison with studies in which the classic WHO/Rose-questionnaire is used as well as studies that use a modern version of this questionnaire.^{8,28,29}

Studies on the prevalence of intermittent claudication in the general population have produced divergent results. The prevalence of IC varies between 0.6 and 6.1 (men: 1.1-7.0, women 0.7-7.4).^{10,13-17,19-21,36,37} Our results for Rose-IC are at the lower end of this range (table 9.2). *Hale et al.* found relatively high prevalence figures in an elderly population, using a definition of IC not strictly meeting the Rose-criteria.^{11,12} Our results for total IC for the age group 65-75 years (men: 10%; women: 8%) correspond quite well with their figures for this age group (7-12%).

Few studies have reported on the prevalence of absent or diminished peripheral pulses. Our results for the prevalence of abnormal pedal pulses (8%) are within the range reported by others (3.2-18%).¹⁶⁻¹⁸

Noninvasive testing

There is no unanimous answer to the question which noninvasive test should be applied in epidemiological studies on PAOD. Population based prevalence studies on PAOD using noninvasive tests can be divided in two groups: those in which a certain cutoff value of the AB-ratio is used as criterion for PAOD and those in which more extensive tests are performed.

In our study the AB-ratio measured with a hand-held Doppler-device was chosen, as explained in the 'Method' section. The reactive hyperaemia test was not used, since its application on a large scale is less feasible in general practice: one session takes about 30-45 minutes and is often painful for the patient. Furthermore, the reproducibility of the reactive hyperaemia test is less than the reproducibility of the assessment of the resting AB-ratio.^{4,18,38-42} Our results (figure 9.1, tables 9.3 and 9.4) are within the range of results found by other authors who used the AB-ratio (cutoff values between 0.75 and 0.95) as criterion for PAOD (3.4 to 14.3%).^{16,18,20,21,43,44}

In the second group of studies prevalence figures are reported to be 11.7%, 13.7% and 8% ('grossly abnormal') to 25% ('moderately and grossly abnormal').^{17,18,19} Aside should be noticed that in the study of *Hiatt et al.* 87% of all PAOD cases were discovered using only the AB-ratio at rest (cutoff value 0.94).¹⁸ In the age group 65-75 years *Criqui et al.*, using extensive noninvasive testing, found a prevalence among men of 12-19%, among women of 12%.¹⁷ *Vogt et al.* (AB-ratio <0.90) found a prevalence of 4% among women of this age group.³⁷ In our study these figures were 16.4% for men and 11.2% for women in this age category. *Ögren et al.* found a prevalence of 14% among men, 68 years of age (AB-ratio <0.90).³⁶ In the study by *Coni et al.*, the prevalence of an AB-ratio lower than 0.75 was 9.1% among 264 patients between 66 and 96 years of age.²⁰ Using this cutoff value in our — younger — population a prevalence of 5.5% was found.

Gender

We know of only one study in which an apparent male predominance of PAOD was reported (gender ratio 1.4-2.0).⁴³ In our study the prevalence of PAOD in men was somewhat higher than in women (gender ratio 1.1). However, manifest atherosclerosis (symptomatic PAOD, IHD, CeAD) occurred significantly more

often in men than in women. Furthermore, among men more often an advanced stage of PAOD was present (more lower AB-ratios, more often surgical interventions).

The results of noninvasive testing in two other studies were similar to ours: PAOD occurred about 1.3 times more often among men.^{17,19} *Fowkes et al.* found a higher mean AB-ratio for men but a larger proportion with an AB-ratio lower than 0.80, which is comparable to our findings (higher mean, larger proportion lower than 0.75).¹⁹ In two other studies no (significant) gender differences were found regarding the height of the AB-ratio.^{16,20} However, *Schroll and Munck* did find a higher prevalence of 'symptomatic' cases (IC, pulselessness, AB-ratio lower than 0.90) among men (3.3% versus 1.0%).¹⁶

Asymptomatic cases

In their study among women between 65 and 93 years of age, *Vogt et al.* found that 18% of all PAOD cases (AB-ratio <0.90) suffered from (Rose)IC.³⁷ *Ögren et al.* found that 15% of all cases of PAOD in his male population of 68-year-olds (AB-ratio <0.90) suffered from (Rose)IC.³⁶ In our study the overall proportion of symptomatic cases (positive IC and noninvasive testing) was 22% and correlated with age, gender (women: 11%) and AB-ratio (tables 9.3 and 9.4). Asymptomatic cases of PAOD differed from symptomatic PAOD cases with regard to gender (more women) and AB-ratio (more higher values), but age distribution and prevalence of concomitant arterial disease did not differ much.

Compared to the population without PAOD, the prevalence of concomitant arterial disease was three to four times as high among asymptomatic PAOD cases. A high prevalence of concomitant atherosclerosis among asymptomatic cases of PAOD was also found in the Edinburgh artery study, where ischaemic heart disease occurred 1.6 times as often among asymptomatic PAOD cases as compared to subjects without PAOD.¹⁹

The results of our study gave rise to a new longitudinal study on the prognosis of PAOD, in which we will further investigate the clinical relevance of asymptomatic cases.

Unknown cases

A British population study in which the patients of two general practices were asked to participate, disclosed that only half of all persons with complaints of claudication had consulted a doctor.⁹ Similarly, *Dormandy* concluded in his review that probably at least half of all patients with intermittent claudication are unknown.⁴⁵

The results of our study show that about two third of all PAOD cases is not known in primary care. As compared to the subpopulation 'known' cases of PAOD, the group 'unknown' PAOD cases could be characterized as: more female, younger, with less complaints, higher AB-ratios and less concomitant arterial disease. It follows that this 'unknown' group mainly represents less advanced cases of PAOD. Still, in the group of PAOD cases with clinically important disease (i.e. an AB-ratio lower than 0.75) 42% of all cases appeared to be unknown to the general practitioner.

Applying these figures to an average Dutch general practice (2350 patients) standardized to the age distribution of the Dutch population (691 patients between

45 and 75 years of age), yields 46 patients with PAOD in this age group, of whom 15 have an AB-ratio lower than 0.75. A total of 32 patients with PAOD will not be registered as such, of whom 6 will have an AB-ratio lower than 0.75.

Although the general practitioner is successful in selecting the worst cases of atherosclerosis for treatment, our results demonstrate that efforts can still be made to improve secondary prevention. Firstly, general practitioners should try to achieve a complete picture of the vascular risk profile of their middle-aged patients. Secondly, in female patients with leg complaints the possibility of PAOD could more often be considered. Finally, a Doppler examination might be useful when taking a careful history and performing a vascular examination in a patient with leg complaints do not yield unambiguous results.

Conclusions

Figures for the prevalence of symptomatic and asymptomatic PAOD differ among studies. This is partly explained by the use of different criteria for intermittent claudication and PAOD.

Although the prevalence of PAOD in men and women is quite equal, men more often suffer from manifest atherosclerotic disease and more often have an advanced stage of PAOD.

Compared to symptomatic PAOD, asymptomatic PAOD is characterized by a higher proportion of women and higher values for the AB-ratio. Compared to subjects without PAOD, symptomatic as well as asymptomatic PAOD correlate with a higher probability of concomitant IHD and CeAD. We confirmed the hypothesis that many cases of PAOD are unknown to the general practitioner. This group of unknown cases mainly represents less advanced cases. Since conservative treatment of PAOD has been proven successful, general practitioners could enhance their efforts towards secondary prevention.

Acknowledgments

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Chapter 10 Predictive value of signs and symptoms for the diagnosis of peripheral arterial occlusive disease in general practice. A multivariable approach.*

Summary *To the general practitioner medical history and physical examination are the major tools for suspecting and establishing the diagnosis peripheral arterial occlusive disease (PAOD). We compared clinical data on PAOD — collected in 18 general practice centres (1340 women, 1115 men, age 40.7-78.4 years) — to the outcome of the measurement of the ankle-brachial systolic pressure ratio (AB-ratio). PAOD was considered to be present if the AB-ratio was below 0.95 on two consecutive occasions (11.5% of all legs). Data were analyzed using multiple logistic regression analysis.*

Three classic features of PAOD appeared to be the most informative diagnostic tests: questioning the patient for intermittent claudication (bivariate diagnostic odds ratio (OR) 5.5, sensitivity 28%, specificity 93%), palpation of both foot pulses (OR 22.7, sensitivity 66%, specificity 80-92%, best single diagnostic procedure) and auscultation of the femoral artery (OR 7.7, sensitivity 27%, specificity 95%). The multivariable ORs were 3.3, 12.8 and 4.1 respectively.

Data like gender (OR 1.3), age above 60 (OR 2.2), unilateral lower skin temperature (OR 2.1), high blood pressure (OR 1.5), a history of smoking (OR 2.2) or the presence of coronary artery disease (OR 1.8) can also significantly contribute to the probability of PAOD. This is particularly relevant in cases that do not represent the classic clinical picture.

Key words *peripheral arterial occlusive disease, diagnosis, noninvasive, general practice, clinical epidemiology*

Introduction

Peripheral arterial occlusive disease (PAOD) is the manifestation of atherosclerosis distal to the aortic bifurcation. PAOD usually has a relatively benign course¹ and conservative therapy of intermittent claudication has proven to be effective.^{2,3} In addition, recognising and treating intermittent claudication will reduce cardiovascular risk in general and contribute to the prevention of coronary artery and cerebral artery disease (CoAD and CeAD). Referral to a vascular specialist can be restricted to progressive cases.^{4,5} However, a progressive course cannot be predicted in individual patients at the time of diagnosis. Therefore regular follow up is neces-

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sary, especially in the first year after diagnosis.^{6,7}

As a consequence, PAOD is relevant to the general practitioner. The role of the general practitioner can be summarized as follows: diagnose adequately, inform the patient properly, start conservative treatment, monitor cardiovascular risk in general, follow up the course of disease, and select efficiently for referral.^{4,5}

Adequate diagnostic management of PAOD presupposes that the doctor knows the significance of available diagnostic procedures. To the general practitioner medical history and physical examination are the major tools for suspecting and establishing the diagnosis of PAOD. The question is: how good are these tools? Some research has been done on the diagnostic value of signs and symptoms in PAOD.⁸⁻¹³ It appears that the negative predictive value (PV-) of a history of intermittent claudication, absent peripheral pulses or a femoral bruit is high.^{9,11,13} However, the positive predictive value (PV+) of each of these diagnostic procedures is rather low.^{11,13} There are few data available on the value of combinations of signs and symptoms.^{9,11,13}

The first objective of the present study was to assess the diagnostic value (sensitivity, specificity, diagnostic odds ratio, predictive values) of single as well as combined data from history, physical examination and patient record (signs, symptoms and vascular risk factors) with regard to PAOD. A second objective was to construct an effective and efficient diagnostic model for the general practitioner.

Methods

General design

The 'Limburg PAOD Study' is a research project conducted by the University of Limburg in Maastricht (the Netherlands) and 22 general practice centres (GPCs) in the region. This project consists of three interrelated studies: a prevalence study, a diagnostic study and an intervention study (on aspirin).^{14,15} The results of the diagnostic study are presented here. Its design is cross-sectional: signs, symptoms and data from the patient record are compared to the outcome of the measurement of the resting ankle-brachial systolic pressure ratio (AB-ratio).

Selection of the study population

Cooperation of GPCs was obtained by means of a lecture and through personal contacts. Eighteen GPCs (31 general practitioners (GPs), 27 practice assistants) decided to take part in the present study.

It is important to realize that in the Netherlands everyone is registered in a general practice. Therefore, the registered population of a general practice is a segment of the general population. The population to be examined by the GP had to approach the 'indicated population', which comprises those patients for whom the GP would feel the need to take a history and perform a physical examination, to rule in or out the diagnosis PAOD. In *table 10.1* is described how the patients for this study were selected. From the registered population patients were selected who were over 40 years of age, who had stated they had 'pain on walking' in a postal questionnaire and who belonged to the 'increased risk' or 'high risk' group (*table 10.1*). Thus, the study population represented a wide spectrum of signs, symptoms and vascular risk.¹⁶

Table 10.1 The selection process

Population		Number
Source population	all patients on the list of 18 GPCs, aged 40 - 75 years received a postal questionnaire with 5 Yes/No questions (pain on walking, smoking ≥ 15 cigarettes, high blood pressure, diabetes, heart disease or TIA/stroke) resulting in a score from 0-5	n = 26620
Responders	response rate 86.4 %	n = 23004
Exclusion	subjects with no 'pain on walking' (n=15342)	
Invited population	selected by a sampling and selection procedure among patients with 'pain on walking' (n=7662)*	n = 3525
Study population	participation rate 69.6%	n = 2455

* a random sample was taken from all patients with a score from 1-5 ('increased risk'); subsequently in each practice remaining patients with the highest scores were selected: all patients with score 5, 4 or 3 and part of the patients with score 2 ('high risk'). This selection procedure was part of the selection process for the Limburg PAOD Study as a whole. Methodological criteria set by the prevalence study and the intervention study had to be taken into account as well.

Data collection

Before visiting their GP's office, each participant filled in an extensive questionnaire addressing symptoms of PAOD, smoking habits and physical exercise. The questionnaire incorporated the WHO/Rose-questionnaire on intermittent claudication,¹⁷ and was differentiated towards specific sensations and sites of leg complaints.

When the patient visited the GP's office, a practice assistant recorded height, weight and blood pressure. The GP read the questionnaire and performed a physical examination: inspection of both legs, palpation of the skin and posterior tibial and dorsalis pedis arteries (ATP, ADP), palpation and auscultation of the femoral arteries. He copied various data from the patient record to the registration form: the presence of CoAD, CeAD, hypertension, hypercholesterolaemia, diabetes mellitus and overweight.

Without knowing the results of the examination by the GP, the practice assistant (or a colleague GP) assessed the AB-ratio of both legs using a pocket Doppler device (Huntleigh Mini Dopplex D500, 8 MHz) and a mercury sphygmomanometer.^{4,18} Systolic pressures were recorded on both arms and legs with the patient lying in supine position in a properly heated examination room. In three solo practices independent assessment of clinical and Doppler data was not feasible and the GP himself performed the pocket Doppler measurement after the physical examination. The AB-ratio was defined as the ankle pressure divided by the highest arm pressure. If the AB-ratio of at least one leg was less than 0.95, the patient was requested to return for a second measurement one week later. All sphygmomanometers were calibrated before the start of the study. The GPs and practice assistants had been trained in performing AB-ratio measurements and reproducibility proved to be satisfactory.¹⁹

Analysis

Definitions

IC was defined as pain or cramps in the calf on walking, disappearing when standing still and not present at rest (typical IC).¹⁷ Also other complaints of the calf showing this ischemic pattern as well as complaints of foot, thigh or buttock showing this ischemic pattern were included in the definition of IC (atypical IC). The categories of other signs and symptoms are listed in the *tables 10.2 and 10.3*.

PAOD was considered to be present in a leg, if the AB-ratio was below 0.95 on two consecutive occasions. This cutoff value was chosen as a balance between the 'specific' cutoff value of 0.90 (sensitivity 75-100%, specificity 80-100%) and the 'sensitive' cutoff value of 1.0 (sensitivity 88-100%, specificity 60-81%) as reported in studies on the validity of the Doppler-method.²⁰⁻²⁴

Bivariate analysis

All analyses were done using BMDP statistical software.²⁵ Bivariate analyses were done to assess the association (diagnostic odds ratio, OR) of each sign or symptom (predictor variable) with the dichotomized outcome of the measurement of the AB-ratio (outcome variable). Significance testing was done using the chi-square test for association.

Variables with a p-value lower than 0.15 (statistical criterion)²⁶ and an OR ≥ 1.5 or < 0.67 (clinical criterion) for left and right legs simultaneously, were entered in the next stage of the analysis. For these selected variables sensitivity, specificity, predictive values and odds ratios were calculated.¹⁶ Since observations of both legs of the same patient cannot be considered to be independent, confidence intervals (95%) of the diagnostic parameters were calculated for left and right legs separately and then averaged.

Multiple logistic regression: selection within clinical clusters

To create a reduced set of candidate variables for the final multiple logistic regression analysis, all selected variables were grouped into six clusters of clinically associated variables: 'age & gender', 'potential symptoms of PAOD', 'inspection and palpation of the skin', 'peripheral pulses', 'risk factors in patient record', 'risk factors in history and physical examination'. Within each of these clusters a logistic regression analysis (stepwise backward) was done. Variables with a p-value lower than 0.05 and an OR ≥ 1.5 or < 0.67 for left and right legs simultaneously, were considered candidate variables for the final logistic regression models.

Multiple logistic regression: final analysis

In order to approach the clinical diagnostic process, the selected variables were regrouped into four subgroups: (1) 'age & gender', (2) 'symptoms of PAOD', (3) 'physical examination', (4) 'risk factors'. Successively four stepwise backward logistic regression analyses were done, starting with subgroup (1), followed by subgroups (1) and (2), then subgroups (1) to (3) and finally subgroups (1) to (4) together. Thus, four successive reduced models were constructed for both legs apart.

After the models of the main effects had been constructed, several potentially relevant first order interaction-terms (e.g. with age and gender) were included in the four models.²⁶ For males the effect of the variable 'erection problems' was tested as

Table 10.2 Diagnostic value of single signs & symptoms. Results of the bivariate analysis (n = 2 x 2455 = 4910 legs; prevalence AB-ratio < 0.95: 11.5% of all legs - *cont. on next page* -

Variable	Categories Neg,Pos	N _{anal}	N _{cat = pos}
Gender	Female, Male	4871	2202
Age group	40-60, 60-80	4868	2336
CoAD (patient record)	No, Yes	4855	1137
CeAD (patient record)	No, Yes	4855	238
Hypercholesterolemia (patient record)	No, Yes	4817	577
Diabetes mellitus (patient record)	No, Yes	4859	495
Intermittent Claudication	No, Yes ^a	4826	453
Smoking (history)	No/stop > 5yrs, Yes/stop < 5yrs	4811	2851
Physical exercise work (history)	Not little, Little	4655	2829
Physical exercise leisure time (history)	Not little, Little	4794	1866
Wounds or sores toes/foot	No, Yes	4855	24
Colour foot/leg	Normal, Abnormal ^c	4843	708
Unilateral lower skin temperature	No, Yes	4670	113
Femoral artery pulse 1	Strong, Absent	4188	68
2	Strong, Weak	4778	658
ATP & ADP pulse 1	Normal, Abnormal ^d	3840	491
2	Normal, Doubt ^d	4356	1007
Femoral artery bruit	No, Yes	4853	353
Quetelet Index (phys. exam.)	≤ 30, > 30	4843	997
Blood pressure (phys. exam.)	Normal, High ^e	4829	1843

^a 'Yes' = typical + atypical IC

^b 42% if a patient meets the criteria for 'typical' IC

^c Abnormal: pale, red or blue;

well. None of these terms contributed statistically or clinically to the models.

In three solo practices independent assessment of clinical and Doppler data was not feasible (14% of all data records). It was tested whether the variable 'independent assessment of clinical and Doppler data' had a significant and relevant effect on the models. This proved not to be the case. Since precision would increase using a larger number of observations, we did not restrict the analysis to the 'independent' data records only.

Up till then all analyses were done for left and right legs separately but decisions to include or exclude a variable were taken simultaneously for corresponding left and right variables. Inclusion in the four final models for both legs combined, was based on statistical significance ($p < 0.05$) and clinical relevance ($OR \geq 1.5$ or < 0.67) for left and right legs simultaneously. Confidence intervals (95%) of odds ratios were calculated for left and right legs separately and then averaged.

The four final models were compared using the likelihood ratio test.²⁶ To visualize the diagnostic performance of each model, receiver operating characteristics (ROC) curves were constructed and the area under the curve (AUC) was estimated.^{27,28} For the most comprehensive model predicted probabilities were calculated (*appendix chapter 10*) and compared to the observed probability of PAOD. The overall fit of this model to the data was assessed by the Hosmer-Lemeshow

shown are the variables that met all analytic criteria)

Diagnostic Odds Ratio (95% ci)	Sens. %	Spec. %	PV+ %	PV- %
1.7 (1.3 — 2.2)	57	56	14	91
3.6 (2.7 — 4.7)	74	55	18	94
3.2 (2.4 — 4.1)	45	79	22	92
3.4 (2.2 — 5.2)	12	96	29	90
1.7 (1.2 — 2.4)	18	89	17	90
2.4 (1.7 — 3.3)	19	91	21	90
5.0 (3.7 — 6.8)	28	93	34 ^b	91
1.8 (1.4 — 2.4)	71	42	14	92
2.0 (1.5 — 2.7)	74	41	14	93
1.6 (1.2 — 2.0)	49	62	14	90
6.7 (2.2 — 21.7)	2	99.7	46	89
3.3 (2.5 — 4.4)	32	88	25	91
5.3 (3.2 — 9.7)	8	98	38	90
6.2 (3.1 — 12.8)	7	99	37	91
3.8 (2.9 — 5.1)	33	89	27	91
22.6 (15.8 — 32.7)	66	92	45	97
7.9 (5.6 — 11.1)	66	80	22	97
7.7 (5.5 — 10.8)	27	95	43	91
0.6 (0.42— 0.86)	14	79	8	88
1.8 (1.4 — 2.3)	51	63	15	91

^d Normal combinations: strong/strong or strong/weak; Abnormal combinations: absent/absent or absent/weak; Doubtful combinations: weak/weak or strong/absent

^e High: systolic pressure > 160 mmHg or diastolic pressure ≥ 95 mmHg.

goodness-of-fit test.^{25,26}

Results

The study population consisted of 1340 women and 1115 men with a mean age of 59.3 years (range: 40.7-78.4). The mean (lowest) AB-ratio was 1.09 (SD 0.17, range 0.20-2.31). Relatively mild disease predominated: only 0.6% of all legs had an AB-ratio < 0.50, 11.5% had an AB-ratio < 0.95.

Table 10.2 shows the results of the bivariate analysis for those predictor variables that fulfilled our criteria for clinical relevance and statistical significance. Overall, the diagnostic procedures with the highest individual diagnostic value (OR) are: palpation of both foot arteries, auscultation of the femoral artery, inspection for wounds or sores on toes and foot, palpation of the femoral artery, comparing the temperature of the skin of both feet, and asking whether or not IC is present. These variables also have a high specificity. Other variables with a high specificity are: a history of CeAD, diabetes or hypercholesterolaemia. An abnormal colour of the skin of the foot is a rather specific sign as well. In general, sensitivity is low but findings with a relatively high sensitivity for PAOD are: a history of little physical

Table 10.3 Variables excluded during the analysis process

Variable	Category: Neg,Pos	Exclusion motive [*]
<i>Excluded during the bivariate analysis:</i>		
Various symptoms while walking, differentiated towards 'site' and 'sensation'	No,Yes	1,4
Various symptoms while resting	No,Yes	1
Complaints of cold feet, unilateral	No,Yes	1
Complaints of cold feet, recent onset	No,Yes	1
Complaints of cold feet, on exercise	No,Yes	1
CoAD or CeAD in the family (history)	No,Yes	1
Amount of walking during work (history)	Not little,Little	1
Unilateral loss of hair foot/leg	No,Yes	1
Ulcer ankle	Medial/No,Lateral	1
Hypertension (patient record)	No,Yes	1
Overweight (patient record)	No,Yes	1
<i>Excluded during LR within clinical clusters:</i>		
Physical exercise during leisure time (history)	Not little,Little	1
Wounds or sores toes/foot	No,Yes	2
Femoral artery pulse 1	Strong,Absent	3
2	Strong,Weak	3
Hypercholesterolaemia (patient record)	No,Yes	1
<i>Excluded during the final LR:</i>		
Physical exercise during work (history)	Not little,Little	1
Colour of foot/leg	Normal, Abnormal	1
Quetelet Index (physical examination)	≤ 30, > 30	1
CeAD (patient record)	No,Yes	1
Diabetes mellitus (patient record)	No,Yes	1
<i>Not included after main effects had been established:</i>		
Erection problems (males) (history)	No,Yes	1
Interactions with 'Age group'	various	1
Interactions with 'Gender'	various	1

^{*} 1: not meeting analytical criteria 2: large confidence interval for each leg apart 3: variables in the cluster 'peripheral pulses' were highly correlated with one another (collinearity)

4: variables that survived the bivariate analysis were replaced by the compound variable 'intermittent claudication', which had the advantage of being easier to interpret clinically

exercise during working activities, being older than 60 years, a history of (recent) smoking, or diminished foot pulses on palpation. PV+ of most variables is also

fairly low, the best predictors of PAOD being the presence of distal wounds or sores, abnormal foot pulses, the presence of a femoral bruit, or suffering from typical IC. The best single predictor of absence of PAOD (high PV-) is a strong pulse of both foot arteries.

Table 10.3 lists the variables that were excluded during the analytical process and provides the reasons for exclusion. *Table 10.4* presents the four final reduced logistic regression models and *figure 10.1* shows the corresponding ROC curves. Each model performs significantly better than the previous one according to the likelihood ratio test. The corresponding AUC show the same pattern.

Using the multivariable models, the predicted probability of PAOD for an individual patient can be estimated (*appendix chapter 10*).²⁶ E.g. using the most comprehensive model, a 62 year old woman with IC, abnormal pedal pulses, and all other 'tests' negative has a probability of 37% to have PAOD in this leg; a 75 year old man with IC, abnormal pedal pulses and a femoral bruit, who smokes, but with a negative outcome of the other 'tests', has a probability of 87% to have PAOD in this leg. Similar calculations can be made using the less differentiated models (*appendix chapter 10*).

The differential diagnostic abilities of the various models can be shown by calculating the minimum and maximum predicted probabilities of each model. In the study population the prior probability of having PAOD is 11%. If age and gender are known (model 1) the predicted — posterior — probability ranges from 3 to 22%. If the general practitioner also knows whether or not IC is present (model 2), this range increases to 3 - 48%. After the physical examination (model 3) the range of predicted posterior probabilities is enlarged to 1-96%. Model 4, though statistically significantly better than model 3, yields a range of predicted probabilities that is only slightly larger (0.6-97%).

In order to see whether the predicted probability of PAOD of the most comprehensive model agreed with the observed probability, the predicted probability was divided in categories of 10% and the observed probability (prevalence) of PAOD was assessed for each category of predicted probability. *Table 10.5* shows that the observed probability of PAOD agreed well with the predicted probability in all but two categories. Likewise, the Hosmer-Lemeshow goodness-of-fit test indicated a reasonable overall fit of this model ($p=0.26$).

Discussion

The results of our bivariate analysis of signs and symptoms traditionally associated with PAOD, show that some of these variables are of no diagnostic relevance, that other variables can have a limited diagnostic function and that some signs, symptoms and vascular risk factors indeed can be used as a diagnostic test. Using a multivariable model that combines the outcome of various relevant diagnostic variables, the general practitioner can estimate the predicted probability of PAOD for an individual patient. The result of this differential diagnostic procedure enables him to evaluate the need for further diagnostic or therapeutic action.

The GPCs where the data for this study were collected were not a random sample of the GPCs in the region around Maastricht. The participants' main motives for cooperation will have been interest in the subject of the study, in (the prevention of) cardiovascular disease and in doing research in general. This will have contribu-

Table 10.4 Diagnostic value of signs and symptoms in the four final reduced logistic models ($N_{LR}=4310$ legs, prevalence of AB-ratio $< 0.95 = 10.7\%$ of all legs)

<i>Model</i> →		<i>1: Age & Gender</i>	
Log likelihood		-1369.6	
Constant		-3.23	
Variables ↓	Categories (Neg,Pos)	$N_{cat=pos}$	OR (95%ci)
Gender	Female, Male	1947	1.9 (1.4-2.5)
Age group	40-60, 60-80	2018	3.7 (2.7-5.1)
Intermittent claudication	No, Yes ^a	397	
Lower skin temperature Left/Right	No, Yes	107	
ATP & ADP pulse	Normal, Abnorm. ^b	424	
	Normal, Doubt ^b	879	
Femoral artery bruit	No, Yes	296	
CoAD (patient record)	No, Yes	957	
Smoking (history)	No, Yes ^c	2557	
Blood pressure (physical examination)	Normal, High ^d	1635	

^a 'Yes' = typical+atypical IC

^b Normal combinations: strong/strong or strong/weak; Abnormal combinations: absent/absent or absent/weak; Doubtful combinations: weak/weak or strong/absent

ted positively to the quality of the data collection, which was performed according to a detailed protocol. A relationship between the selection of the GPs and the clinical characteristics of their registered population cannot be assumed. Therefore, it seems unlikely that a 'GP-selection bias' has occurred.

We aimed at creating a study population that would represent a wide spectrum of signs, symptoms and vascular risk.¹⁶ If selecting the patients for this study would have been the GP's responsibility, this might have resulted in an over-representation of symptomatic and typical PAOD patients. Furthermore, data collection or even patient selection during consulting hours would not have been appreciated by the GPs and would have led to a slower process of data collection and a smaller number of patients.

In this study the diagnostic criterion for the presence of PAOD was a value for the pocket-Doppler AB-ratio lower than 0.95, measured on two consecutive occasions. In other studies where traditional clinical evaluation of PAOD had been compared to the results of noninvasive testing, cutoff values for the resting AB-ratio were chosen between 0.80 and 0.95.⁸⁻¹² In a recent population study an AB-ratio lower than 0.94 was defined as abnormal.¹³ In recent surveys on the prevalence of PAOD cutoff values for the AB-ratio were chosen in the range between 0.75 and 0.97.²⁹⁻³⁴ Using a cutoff value for the AB-ratio lower than 0.95, would imply that

2: (1)+History	3: (2)+Physical Exam.	4: (3)+Risk Factors		
-1310.6 -3.46	-1030.5 -4.42	-1002.4 -5.06		
OR (95%ci)	OR (95%ci)	OR (95%ci)	/	logistic coefficient
1.7 (1.3-2.3)	1.7 (1.3-2.4)	1.3 (0.9-1.8)	/	0.25
3.5 (2.6-4.8)	2.2 (1.6-3.1)	2.2 (1.5-3.2)	/	0.78
4.3 (3.1-6.2)	3.5 (2.3-5.4)	3.3 (2.2-5.1)	/	1.18
	2.1 (1.1-4.2)	2.1 (1.0-4.1)	/	0.72
	14.0 (9.1-21.7)	12.8 (8.4-20.2)	/	2.55
	7.0 (4.8-10.2)	6.6 (4.5-9.8)	/	1.89
	4.6 (2.9-7.2)	4.1 (2.6-6.4)	/	1.40
		1.8 (1.2-2.5)	/	0.56
		2.2 (1.5-3.3)	/	0.80
		1.5 (1.1-2.2)	/	0.42

^c No: never smoked or stopped for longer than 5 yrs; Yes: currently smoking or stopped for shorter than 5 yrs

^d High: systolic pressure > 160 mmHg or diastolic pressure ≥ 95 mmHg

the multivariable models would predict a more advanced stage of PAOD. In primary care it is important to diagnose also less advanced stages of PAOD. Therefore the cutoff value of the AB-ratio should not be chosen too low.

The reactive hyperaemia test was not applied, since its disadvantages make this test less feasible for use in general practice: one session takes about 30-45 minutes and is often painful for the patient. Furthermore, the reproducibility of the reactive hyperaemia test is less than the reproducibility of the measurement of the resting AB-ratio.^{13,35-40}

Although our multiple logistic regression models can easily be written into a spreadsheet programme on a personal computer, the resulting estimates of predicted probabilities in individual patients should not be used in an absolute way. The population of an individual general practitioner may be similar to, but will not be the same as our study population. Methodological choices we made with regard to the cutoff value for the AB-ratio and the selection of variables for the multiple logistic regression analyses, influence the absolute and relative magnitude of the coefficients in the models. Furthermore, although table 10.5 shows there is good agreement between observed and predicted probabilities of PAOD, our model is not yet 'validated' in a new population and thus may tend to perform in an optimistic way. The variables that finally were included in the logistic regression models

Figure 10.1 ROC Curves of the four final reduced logistic models ($N_{LR}=4310$ legs)

Model 1: Age & gender	AUC=0.686
Model 2: (1) + History	AUC=0.723
Model 3: (2) + Physical examination	AUC=0.861
Model 4: (3) + Risk factors	AUC=0.868

Table 10.5 Observed probability in categories of predicted probability of the most comprehensive logistic model (model 4)

Categories of Predicted Probability of PAOD	Observed Probability (%)
$0 \leq 10\%$	3.0
$10 \leq 20\%$	12.6
$20 \leq 30\%$	24.6
$30 \leq 40\%$	34.1
$40 \leq 50\%$	52.0
$50 \leq 60\%$	57.1
$60 \leq 70\%$	60.3
$70 \leq 80\%$	73.5
$80 \leq 90\%$	81.6
$90 \leq 100\%$	88.2

were selected both on clinical relevance and statistical significance and the presence or absence of these variables will contribute to differential diagnosis in an individual patient.

The results of our bivariate analyses show that some signs and symptoms traditionally associated with PAOD do not have a statistically significant diagnostic relevance, e.g. complaints of cold feet, unilateral loss of hair on foot or leg, a lateral ankle ulcer (*table 10.3*). Some procedures are relevant when used as a single test but their diagnostic value is reduced when used in combination with other, more powerful diagnostic procedures. E.g. inspection for sores or wounds, and palpation of the femoral artery. This is partly due to the low prevalence of an abnormal ('positive') test result of these features. Other diagnostic procedures are characterized by either a relatively high sensitivity (age, history of smoking, history of physical exercise during working activities) or a relatively high specificity (inspection of the feet for wounds or sores, palpation of the femoral artery pulse, palpation of the temperature of the skin; *table 10.2*).

Few studies have been done where traditional clinical evaluation of PAOD was compared to the results of noninvasive testing.^{8,13} Only the results of studies in which the study population was not highly selected can be indicative for general practice.^{9,11,13} In these studies the sensitivity of typical IC¹⁷ varies between 9 and 19% and specificity is reported to be 99%.^{9,11} If 'possible' or 'probable' IC is accounted for as well — comparable to our definition of IC — sensitivity varies from 8 to 20% and specificity is 96%.^{11,13} Our results were higher for sensitivity (28%) and lower for specificity (93%).

In stead of the compound variable IC, we initially analyzed the diagnostic value of various leg complaints appearing on walking, differentiated towards specific site and sensation. Thus we hoped to identify a cluster of leg complaints with a higher sensitivity than positive 'Rose-claudication'.¹⁷ However, in accordance with the results of the Edinburgh Artery Study, a differentiated description of the pain or discomfort in the leg did not have diagnostic relevance.⁴¹

The results of *Criqui et al.* for the presence of a femoral bruit (sensitivity 20%, specificity 96%) were similar to our findings (27% and 95% respectively).¹¹

Our results for sensitivity and specificity of absent or diminished foot pulses (sensitivity 66%, specificity 80-92%) were in the range of values found by other authors (sensitivity 5-71%, specificity 73-97%).^{9,11,13} In each of the studies mentioned here, the sum of sensitivity and specificity of the palpation of the foot pulses was higher than that of the other clinical diagnostic procedures, making it the best single clinical diagnostic procedure.⁴² We can confirm that palpation of both pedal pulses is the best single diagnostic procedure: specificity and PV- are high and sensitivity and PV+ are relatively high.

The results of the bivariate and multivariable analyses in this study (*tables 2 and 4*) show that in particular palpation of the foot arteries, auscultation of the femoral artery and questioning the patient for IC are the signs and symptoms that can be used as diagnostic tests. Our most comprehensive regression model reveals that apart from these classic clinical diagnostic procedures, data on gender, age (above 60), unilateral lower skin temperature, high blood pressure, a history of (recent) smoking and the presence of CoAD can increase or decrease the probability of PAOD being present (*table 10.4*). This information will be particularly relevant in cases that do not represent the classic clinical picture of IC with absent foot pulses

and a femoral bruit. E.g. in our population (prior probability of PAOD: 11%) a 56 year old man with intermittent claudication but doubtful pedal pulses has a predicted probability of PAOD of only 15% if all other 'tests' of model 4 are negative, but the probability increases to 28% if he also smokes, to 37% if he smokes and his blood pressure is too high, and to 51% if he smokes, has a high blood pressure and suffers from coronary artery disease. For a woman of the same age these figures would be 12%, 23%, 32% and 45% respectively. These examples demonstrate that it is important for the general practitioner to know the cardiovascular risk profile of his patients.

The multivariable models support the intuitive estimate of the probability of PAOD the general practitioner will have after each stage of his clinical evaluation of the patient. In many patients he will be able to rule out disease with a high degree of certainty (e.g. 60% of all legs in our study population had a predicted probability of PAOD < 0.05). In a small group of patients he can reach a high degree of certainty that PAOD is present and he will feel confident to discuss conservative measures with the patient (e.g. 1.3% of all legs in our study population had a predicted probability of PAOD > 0.8). If the probability of PAOD is not low enough to exclude disease but not high enough to establish the diagnosis PAOD (e.g. in our study population 38% of all legs had a predicted probability of PAOD between 0.05 and 0.80), the general practitioner might consider noninvasive testing to resolve his diagnostic uncertainty.^{4,5}

In conclusion, it would be useful to realize an external validation of our models by testing their performance in a similar study population. Our current analysis indicates that traditional clinical evaluation enables the general practitioner to decide upon the need for further diagnostic or therapeutic action. The classic features of PAOD appear to be the most informative diagnostic tests: questioning the patient for IC, palpation of both foot pulses and auscultation of the femoral artery. But also various other data from history, physical examination and patient record can significantly influence the probability of PAOD being present. This information will be particularly relevant in cases that do not represent the classic clinical picture.

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Chapter 11 General discussion

Summary *In this chapter the main results of this study are discussed in relation to our objectives and the literature. Various methodological issues are summarized. The implications of our results for general practice are formulated and some ideas on future research in this field are presented.*

The present study demonstrates that in many cases the general practitioner can reject or confirm the hypothesis that PAOD is present, on the basis of medical history, physical examination and the vascular risk profile of a patient. If this is not possible, the general practitioner can use the hand held Doppler device for measuring the AB-ratio, a valid and reproducible supplementary test, to reduce his diagnostic uncertainty. Practical decision rules for the measurement and interpretation of the AB-ratio are provided.

The results of the present study can contribute to good agreements between general practitioners, vascular function departments and vascular specialists on the use of noninvasive diagnostic techniques for PAOD.

The notion that PAOD is a manifestation of systemic atherosclerosis should have practical implications for the general practitioner. This study shows that there are possibilities for the general practitioner to optimize his performance with regard to the secondary prevention of cardiovascular disease.

In the near future we hope to publish results on the conservative treatment of PAOD, prognostic indicators and the relevance of asymptomatic disease. An alternative approach to the analysis of diagnostic data could be tested using our data set.

More studies on the quality of life in PAOD patients are required. It would also be worthwhile to study the effect of the use of the Doppler device in primary care on the quantity, quality and outcome of referrals to the vascular specialist.

Above all, practice based research on PAOD requires consistent definitions and codes for PAOD. In general, practice based epidemiologic research of chronic diseases is possible only if everyday clinical data are collected according to research standards. This will be facilitated when computerized protocols that easily can be integrated in the daily routine of the general practitioner will become available.

In this chapter the main results of our studies will be discussed in relation to the objectives formulated in chapter 4 and be compared to recent literature.* Subsequently, various methodological issues will be summarized. Finally, we will outline the implications of our results for general practice and conclude this chapter with some ideas on future research in this field.

* Recent literature was gathered according to the methods described in the chapters 2 and 3. In this chapter publications from 1990 up till august 1994 will be discussed.

Aims, results & recent literature

PREVALENCE

Aims

Reviewing the literature on the prevalence of peripheral arterial occlusive disease (PAOD), generated a number of topics for further investigation (*chapter 2*).

A population study using noninvasive testing reported a much higher prevalence (11.7%) of PAOD as compared to the data derived from general practice morbidity registrations (0.2-0.7%) and population studies using questionnaires on intermittent claudication (1.7-4.8%).

In contrast with general medical belief the prevalence of objectively diagnosed PAOD in women was reported to be not much lower than the prevalence of PAOD among men. If this is true, the question arises whether PAOD possibly has a more benign course in women, i.e. do women with PAOD generally present with a less advanced stage of the disease?

Moreover, the literature suggested that there were many asymptomatic patients and patients with atypical complaints. Compared to patients without PAOD, asymptomatic cases were reported to have a high prevalence of cardiovascular comorbidity. This would make screening or case finding in subjects without complaints more appropriate.

Many patients (50% or more) with PAOD appeared not to be known as such to their general practitioner. The relevance of this 'tip of the iceberg' phenomenon was not clear: are unknown PAOD cases' important from a therapeutic or preventive perspective?

Our first research question was: 'What is the prevalence of PAOD in the general practice population, and how large are the categories 'asymptomatic', 'atypical' and 'manifest' PAOD, known and unknown to the general practitioner?' (*chapter 4*).

Results

In *chapter 9* we described our study on the prevalence of PAOD in a stratified sample of 3171 patients aged 45-75 years, who were on the list of 18 general practice centres. Results were recalculated for the base population of these general practice centres (18884 patients aged 45-75 years) and are summarized here. PAOD was considered to be present in a patient, if the ankle-brachial systolic pressure ratio (AB-ratio) of at least one leg was lower than 0.95 on two consecutive occasions (interval of one week). The AB-ratio was defined as the arm systolic pressure (brachial artery) divided by the ankle systolic pressure (posterior tibial or dorsalis pedis artery). Pressures were assessed with a hand held Doppler device and a sphygmomanometer.

The difference in prevalence figures provided by epidemiological studies can be explained partly by the use of different criteria for intermittent claudication and PAOD. In our study we can demonstrate this phenomenon. In our population the prevalence of 'Rose-claudication'¹ is 1.6%, the prevalence of 'definite (calf) intermittent claudication'^{2,3} is 5.3% and the prevalence of all ischemic leg complaints on walking ('total intermittent claudication') is 6.6%.

Our bivariate analyses of high risk groups identifiable to the general practitioner, confirmed once more that the prevalence of PAOD is higher among patients with

hypertension (relative risk* 2.8), hypercholesterolemia (relative risk 2.0), diabetes mellitus (relative risk 3.3) or patients with a history of smoking (relative risk 1.7).

Although the prevalence of PAOD in men (7.2%) and women (6.5%) is quite equal (male:female = 1.1), men more often suffer from manifest atherosclerotic disease (male:female ratio for symptomatic PAOD: 3.3; for PAOD with concomitant ischemic heart disease or cerebrovascular disease: 2.6) and more often have an advanced stage of PAOD (male:female ratio for AB-ratio < 0.75: 2.6).

Compared to symptomatic PAOD, asymptomatic PAOD is characterized by a higher proportion of women (57% is female versus 25% among symptomatic PAOD) and by higher values for the AB-ratio (only 22% with an AB-ratio < 0.75, versus 69% among symptomatic cases). Compared to subjects without PAOD, subjects with symptomatic or asymptomatic PAOD have a higher probability to suffer from concomitant ischemic heart disease (relative risk = 3) and cerebrovascular disease (relative risk = 4).

We confirmed the hypothesis that many cases of PAOD are unknown to the general practitioner (68%). Among these unknown cases female and young patients are relatively overrepresented (60% female, 58% younger than 65 years) as are less advanced cases: only 20% with an AB-ratio < 0.75, only 15% symptomatic cases and only 24% with concomitant ischemic heart disease or cerebrovascular disease.

Recent literature

Eleven recent population studies with data on the prevalence of PAOD in moderately selected populations were found.⁴⁻¹⁴ These publications were already discussed in relation with our findings in *chapter 9*.

A relevant issue, addressed in a number of publications, is the possible significance of asymptomatic PAOD. In an extensive review by *Vogt et al.* it was concluded that detection of asymptomatic PAOD in the elderly is important because it can provide a rapid and easy indicator of the degree of systemic atherosclerotic cardiovascular disease, and thereby identify individuals at high risk for mortality and morbidity.¹⁵ *Newman et al.* demonstrated an inverse relation of the AB-ratio with cardiovascular risk factors and the presence of subclinical and clinical cardiovascular disease. Even asymptomatic patients with modest reductions in the AB-ratio (0.8-1.0) appear to be at increased risk of cardiovascular disease.⁹ In a prospective study *Criqui et al.* demonstrated that among asymptomatic PAOD patients the cardiovascular mortality was much higher as compared to subjects without PAOD.¹⁶

CLINICAL DIAGNOSIS

Aims

Reviewing the literature on the diagnostic value of medical history and physical examination with regard to PAOD (*chapter 2*), revealed that the knowledge in this field is fragmentary. Although medical textbooks give long lists of clues to support the diagnosis PAOD (medical history, inspection, palpation, auscultation) quantitative data to support this knowledge are sparse.

* relative risk: occurrence of disease when determinant is present, divided by the occurrence of disease when determinant is absent

Furthermore, medical textbooks with regard to PAOD are usually written by medical specialists, i.e. vascular specialists, and are based on their experience with more advanced stages of PAOD. The question may be posed whether the classic textbook pattern of PAOD should be modified for the general practitioner.

Although the specificity of intermittent claudication (meeting the WHO-criteria) was reported to be high (99%), the sensitivity appeared to be quite low (9%). This raised the question whether the sensitivity of the medical history could be improved, e.g. by differentiating leg complaints towards site and sensation or by adding questions concerning risk factors. Data on the diagnostic significance of abnormal peripheral pulses or a femoral bruit were limited and showed a pattern similar to intermittent claudication: a fairly low sensitivity (13-71%) and an acceptable specificity (73-98%). On the diagnostic value of combined data from history and physical examination, almost no data were available.

Our second research question was: 'What is the value of clinical data (history, physical examination, patient record) for the diagnosis of PAOD?' Or: 'What are the sensitivity, the specificity and the predictive values of clinical data — separately and combined — in relation to PAOD?' (*chapter 4*).

Results

In *chapter 10* our study on the diagnostic value of signs and symptoms associated with PAOD is described. Using both bivariate analyses and multiple logistic regression, clinical data of 3654 patients aged 40.7-78.4 years (mean age 59.3 years) were compared to the outcome of Doppler ankle pressure measurements.

The results of the bivariate analyses show that some signs and symptoms traditionally associated with PAOD do not have a statistically significant diagnostic relevance. E.g.: complaints of cold feet, unilateral loss of hair on foot or leg, a lateral ankle ulcer (*table 10.3*).

Some clinical signs are relevant when used as a single test but their independent diagnostic value is reduced when they are used in combination with other signs or symptoms. E.g.: inspection for sores or wounds, colour of foot or leg, palpation of the femoral artery, history of cerebrovascular disease, history of diabetes, history of hypercholesterolaemia. This phenomenon is partly explained by the low prevalence of an abnormal ('positive') test result of these features. The sensitivity of these features also is relatively low (*table 10.2*).

Other diagnostic procedures are characterized by either a relatively high sensitivity (age, history of smoking, history of (little) physical exercise during work) or a relatively high specificity (inspection of the feet for wounds or sores, palpation of the femoral artery pulse, palpation of the temperature of the skin; *table 10.2*).

Some signs, symptoms and vascular risk factors indeed can be used as a diagnostic test. The results of the bivariate and multivariable analyses in this study (*tables 10.2-10.4*) show that in particular palpation of the foot arteries, auscultation of the femoral artery and questioning the patient for intermittent claudication — the three classic features of PAOD — are the signs and symptoms that can be used as diagnostic tests. We could confirm the results of other studies that showed that palpation of both pedal pulses is the best single diagnostic procedure: specificity and negative predictive value are high, and sensitivity and positive predictive value are relatively high.

In stead of the compound variable intermittent claudication, we initially analyzed

the diagnostic value of various leg complaints appearing on walking, differentiated towards specific site and sensation. Thus we hoped to identify a cluster of leg complaints with a higher sensitivity than positive 'Rose-claudication'. However, a differentiated description of the pain or discomfort in the leg did not have diagnostic relevance. This result is in accordance with the experience described by *Leng et al.* who tried to improve the WHO/Rose-questionnaire for intermittent claudication.^{2,3}

Our most comprehensive logistic regression model revealed that besides the classic clinical diagnostic trio, data on gender (male), age (above 60), unilateral lower skin temperature, high blood pressure, a history of smoking and the presence of ischemic heart disease can increase the probability of PAOD being present (*table 10.4*).

Recent literature

Data on the diagnostic value of complaints of intermittent claudication were found in three recent articles.^{6,10,11} The study of *Hiatt et al.* was discussed in *chapter 10*. In the study of *Skau and Jönsson* (353 men and women aged 50-89 years) a modified definition of intermittent claudication was used. From their 2×2 table comparing the presence of intermittent claudication with the AB-ratio (cutoff value 0.80), the diagnostic odds ratio of intermittent claudication could be recalculated as 4.7 (sensitivity 42%, specificity 87%).¹⁰ A similar calculation performed with the data of *Ögren et al.*, who studied a population of 477 men aged 68 years, resulted in a diagnostic odds ratio of Rose-claudication of 8.8 (sensitivity 15%, specificity 98%) when compared to the AB-ratio (cutoff value 0.90).¹¹

The value of the vascular physical examination was addressed in five papers.^{6,17-20} The study of *Hiatt et al.* was discussed earlier. In two British studies the inter-observer agreement and accuracy of the palpation of the foot pulses was assessed. In one study four observers (consultant, registrar, senior house officer, vascular clinic nurse) examined 33 patients with intermittent claudication. There was 67% agreement in palpation of the dorsalis pedis pulse, and 53% agreement in palpation of the posterior tibial pulse, suggesting that the dorsalis pedis pulse is easier to palpate than the posterior tibial pulse.¹⁷ In the second study fifty observers (surgeons, other doctors, medical students) examined the femoral and distal pulses of four patients with PAOD and one asymptomatic subject. Using the consensus diagnosis of two vascular surgeons as a reference, there were 10% false positive (not palpable when present) and 10% false negative (palpable when absent) outcomes.¹⁸

In the study of *Nicholson et al.*, 37 limbs of 50 symptomatic patients (43 presenting with intermittent claudication, seven with rest pain) referred to an outpatient surgery department were studied. The presence of an arterial bruit in the iliac, femoral or popliteal artery was compared to the outcome of arteriography. The odds ratio for 'any bruit' could be recalculated as 12. The predictive value of a bruit for PAOD confirmed at arteriography, was 87% in this small, selected population.¹⁹

Endean et al. reported a considerable inaccuracy in both performance (total score: 63% correct, predefined minimum score: 70%) and interpretation of the vascular physical examination performed by interns and medical students.²⁰

In conclusion, recent studies on the diagnostic value of a history of intermittent

* positive test: pulse not palpable; negative test: pulse palpable

claudication confirmed the results from formerly reviewed studies and our study: this symptom has a low sensitivity and a high specificity. Recent studies on the inter-observer agreement and accuracy of the physical vascular examination confirm the conclusions of our previous review that there is considerable disagreement among doctors whether a particular pulse is palpable or not. Yet, in our study as well as in other studies, the physical examination proved to have a high diagnostic value.

ANKLE-BRACHIAL SYSTOLIC PRESSURE RATIO

Aims

While preparing our main study, the literature on noninvasive tests for PAOD was reviewed. We were particularly interested in the measurement of the ankle-brachial systolic pressure ratio because of its assumed feasibility in general practice (*chapter 3*).

Many older studies on the reproducibility of the measurement of the ankle-brachial systolic pressure ratio (AB-ratio), appeared to be of limited value: the method used to determine the reproducibility was usually described insufficiently; the parameters used to represent the reproducibility were not uniform and may not simply be compared; the observers were generally experienced staff members of surgical departments or vascular laboratory technicians rather than general practitioners or general practice assistants. From the literature we estimated that the preferable 95% prediction interval of the AB-ratio comprised the measured value ± 0.14 - 0.2 . The difference between two measurements of the AB-ratio on different occasions had to be larger than 0.15 to be statistically significant and clinically relevant.

The assessment of the validity of ankle pressure measurements for general practice on the basis of the literature, was encumbered by several factors. All research was carried out in surgical or medical (outpatient) departments rather than in primary health care settings. In the specialist's office there will be few or no patients in an early phase of PAOD. In general, tests were performed on persons with complaints. For 'controls' either 'healthy' volunteers (i.e. without complaints) or the 'healthy legs' of patients with PAOD were used. When the control group consisted of 'healthy' volunteers, angiography was usually not performed on these subjects, whereas in patients it was. By contrast, when the control group comprised 'healthy legs' of patients with PAOD, an angiogram was made. The issue of independency of Doppler testing and angiogram was only rarely discussed explicitly. Usually the noninvasive tests were performed before angiography. It was not always clear whether the data were examined prospectively or retrospectively.

Study of the literature demonstrated that the choice of a cutoff value for the AB-ratio was open to discussion: there appeared to be a grey zone between the 'specific' cutoff value of 0.90 and the 'sensitive' cutoff value of 1.0 . The figures for sensitivity and specificity in most studies were high, but varied among studies.

We decided to investigate the reproducibility and the diagnostic validity of the measurement of the AB-ratio for the general practice setting. The following research questions concerning the measurement of the AB-ratio, were formulated (*chapter 4*):

- what is the magnitude of the measurement variation due to the multi-observer design of the Limburg PAOD Study?

- what is the magnitude of other sources of measurement variation, relevant to clinical situations?
- what is the accuracy and diagnostic value of the measurement of the AB-ratio?
- what is its optimum cutoff value?
- can we provide threshold cutoff values beyond which PAOD can be ruled in (high positive predictive value) or out (high negative predictive value)?

Results

In *chapter 7* we described our study on the reproducibility of the measurement of the AB-ratio in general practice. Fifty-nine observers performed 503 AB-ratio measurements on nine patients over a period of nine weeks. The magnitude of the inter-observer error (SD 0.114) was comparable to other studies. The contribution of the systematic measurement variation of each observer ('observer bias') was low (SD 0.044). This implies that multi-observer studies using AB-ratio measurements are only slightly less efficient than a hypothetical single observer study. Our results for the intra-observer error were slightly higher than the results of other studies (SD 0.105).

In *chapter 8* we reported on our study on the diagnostic power of the measurement of the AB-ratio. Single and repeated AB-ratio measurements performed in three general practices were compared to the outcome of measurements by a specialized vascular laboratory (single measurements: 231 legs of 117 patients; repeated measurements in a subgroup of 92 legs of 51 patients). ROC analysis showed that the outcome of (three) repeated measurements leads to more valid results than single measurements of the AB-ratio. The optimum cut off value for the AB-ratio was calculated as 0.92 (sensitivity 87%, specificity 91%, accuracy 90%) in the case of three repeated measurements. In case of a single measurement the AB-ratio performed less well, but still acceptable. The optimum cut off value was 0.97 (sensitivity 79%, specificity 82%, accuracy 81%). We calculated threshold cutoff values for high predictive values for a positive and negative test outcome: the positive predictive value is higher than 95% if the AB-ratio (mean of three) is lower than 0.88; the negative predictive value is higher than 99% if the AB-ratio (mean of three) is higher than 0.98.

Recent literature

Five recent publications on noninvasive testing contained data on the diagnostic value of the AB-ratio. We have referred earlier to two of these publications.^{6,21} *Baxter and Polak* found a high sensitivity and accuracy of the AB-ratio (standard: angiography) but their study population was small and highly selected.²² *Nilsson et al.* compared a combination of noninvasive tests to computer-assisted arteriography and concluded that the AB-ratio was the single variable (out of 5 noninvasive tests) most closely correlated to the likelihood of arterial occlusions.²³ *Newman et al.* analyzed the occurrence of cardiovascular risk factors, noninvasive signs of cerebral or cardiac disease and manifest cardiovascular disease for four levels of the AB-ratio ($\geq 1 < 1.5$, $\geq 0.9 < 1.0$, $\geq 0.8 < 0.9$, < 0.8) in a population of 5084 subjects aged 65 years or older. They found an inverse relation of the AB-ratio with cardiovascular risk factors, subclinical and clinical cardiovascular disease. Even asymptomatic patients with modest reductions in the AB-ratio (0.8-1.0) appeared to be at increased risk of cardiovascular disease. The occurrence of reported hypertension, current

smoking, carotid plaque, major ECG abnormality, angina pectoris and myocardial infarction was significantly higher among subjects with an AB-ratio between 0.9 and 1.0 as compared to subjects with an AB-ratio above 1.0.⁹

In conclusion, the results of these recent studies support our conclusion that measuring the AB-ratio is a valid diagnostic method and a marker of overall atherosclerosis.

Methodological issues

In this section the most important methodological issues of our studies will be discussed. Detailed discussions are presented in the *chapters 7-10*.

PREVALENCE

The general practice centres where the data for the prevalence and diagnostic studies were collected, were not a random sample of the general practices in the region around Maastricht. Yet, it seems unlikely that a 'GP-selection bias' has occurred (*chapter 10*).

The methodological crux of our study on the prevalence of PAOD was the complex stratified sampling procedure, necessary to meet the demands of all parts of the 'Limburg PAOD Study' in an efficient way (*chapter 5*). Complex sampling implied complex recalculations (*chapter 9*).

There is no unanimous answer to the question which noninvasive test should be applied in epidemiological studies on PAOD. In our studies the diagnostic criterion for the presence of PAOD was a value for the pocket-Doppler AB-ratio lower than 0.95, measured on two consecutive occasions. In the prevalence study this relatively high cutoff value was appropriate because in primary care a sensitive cutoff value is important in order to detect early stage cases to be evaluated further.

Prevalence figures and their confidence intervals for the general population had to be recalculated from the stratum specific data yielded by the study population to the population of patients who had responded to the postal questionnaire. Formulas for weighted means of stratum-specific prevalences and confidence intervals were entered into a spreadsheet programme (*chapter 9*). The formulas and an example for one variable are given in the *appendix* of chapter 9.

CLINICAL DIAGNOSIS

In the study on the diagnostic value of signs and symptoms associated with PAOD (*chapter 10*), we aimed at creating a study population that would represent a wide spectrum of signs, symptoms and vascular risk.²⁴ Selecting the so-called 'indicated population'²⁵ (or 'clinically relevant population', i.e. the sub-population of patients with leg complaints that visit their general practitioner, of whom the latter wants to take a specific history aimed at establishing or ruling out PAOD) was not feasible in daily practice, would have led to a slower process of data collection and a smaller number of patients, and might have resulted in an over-representation of symptomatic and typical PAOD patients.

The goal of the multiple logistic regression analysis was to reduce the total number of possible diagnostic variables ('tests') to an effective minimum number, i.e. to

define the most efficient combination of signs and symptoms. The variables that finally were included in the logistic regression models were selected both on clinical relevance (odds ratio ≥ 1.5 or < 0.67) and statistical significance ($p < 0.05$). Consequently, the presence or absence of these variables indeed will contribute to differential diagnosis in an individual patient. Although we demonstrated good agreement between observed and predicted probabilities of PAOD, our models are not yet 'validated' in a new, similar population and thus may tend to perform in a too optimistic way.

ANKLE-BRACHIAL SYSTOLIC PRESSURE RATIO

In the Doppler reproducibility study (*chapter 7*), the intra-observer error could be estimated indirectly from a random effects analysis of variance model.^{26,27} To obtain a direct estimate of the intra-observer error, ideally one needs independent repeated measurements of the same patient by the same observer. This can be achieved using random-zero sphygmomanometers.

In the Doppler validity study (*chapter 8*) the study population was selected from a cohort of the Limburg PAOD Study. The spectrum of PAOD and co-morbidity in this population was appropriate: relatively mild disease predominated and sufficient non-arterial leg complaints were present as well.²⁴ In theory the ideal study population would have been the 'indicated population', i.e. the sub-population of patients who visit their general practitioner and of whom the clinical picture (medical history, physical examination) motivates the general practitioner to perform a Doppler measurement.

The 'gold standard' in this study was the consensus diagnosis made by two experienced vascular laboratory technicians on the basis of the results of a combination of noninvasive tests. Duplex scanning was not used in this gold standard because it was not our aim to establish the exact site of an arterial obstruction or stenosis.

Implications for general practice

DIAGNOSTIC MANAGEMENT OF PAOD

Previously, patients with PAOD often have been referred to vascular surgeons for diagnosis and long-term care despite the fact that the majority were managed conservatively.²⁸ The role of the primary care physician for these patients is evident: he is the principal health care provider responsible for the conservative management of these patients.²⁹ Appropriate management of PAOD should start with a thorough clinical investigation including ankle pressure measurements.²⁸

Signs, symptoms and risk profile

When a patient with leg complaints visits his general practitioner, the latter has to come up with a diagnosis. Our multivariable diagnostic models (*chapter 10*) may support this process by quantifying the feeling of certainty on the diagnosis PAOD the general practitioner will experience after he has taken a medical history and performed a physical examination. In the *figures 11.1 and 11.2* some examples are given of the predicted probability of PAOD when data from history and physical examination are combined. These examples stress the diagnostic importance of

Figure 11.1 Predicted probability of PAOD (%) using information from medical history and physical examination (based on the multivariable diagnostic models 1-3 described in chapter 10)

Figure 11.2 Some examples of the predicted probability of PAOD (%) using information from medical history, physical examination and patient record (based on the multivariable diagnostic models 1-4 described in chapter 10)

performing a physical examination. If only the fact that a patient suffers from intermittent claudication is taken into consideration, the predicted probability of PAOD will never exceed 50%.

Our results demonstrate that on the basis of history and physical examination the general practitioner will often be able to rule out disease with a high degree of certainty (e.g. 60% of all legs in our study had a predicted probability of PAOD < 5%). In a small group of patients he can reach a high degree of certainty that PAOD is present (e.g. 1.3% of all legs in our study had a predicted probability of PAOD > 80%) and he will feel confident to discuss conservative measures with the patient. If the probability of PAOD is not low enough to exclude disease but not high enough to establish the diagnosis PAOD (e.g. in our study 38% of all legs had

Table 11.1 Decision rules for the measurement and interpretation of the pocket Doppler AB-ratio (in the range of prior probabilities of 5-33%)

AB-ratio	Action	Interpretation
AB-ratio > 1.09	even if single measurement:	no PAOD (99% certain)
AB-ratio 0.75-1.09	repeat measurement (e.g. 2 more times): - if mean AB-ratio > 0.98: - if mean AB-ratio < 0.88: - if mean AB-ratio 0.88-0.98:	no PAOD (99% certain) PAOD (95% certain) the higher the prior probability that PAOD is present the higher the AB-ratio has to be to rule out disease*
AB-ratio < 0.75	even if single measurement:	PAOD (95% certain)

* e.g. if the prevalence is 5% then the AB-ratio has to be > 0.88 and if the prevalence is 10%, then the AB-ratio has to be > 0.94 to rule out PAOD

a predicted probability of PAOD between 5 and 80%)., the general practitioner might consider noninvasive testing to resolve his diagnostic uncertainty.

Doppler measurement

On the basis of our study on the diagnostic performance of the AB-ratio measured with a hand held Doppler device, practical decision rules for the use and interpretation of the Doppler method in general practice could be derived for the range of prior probabilities of 5-33% (*table 11.1*). To maximize diagnostic performance one ought to measure the AB-ratio on more than one occasion before reaching a definite diagnostic conclusion. Thus, the range of less conclusive AB-ratios is reduced to values between 0.88 and 0.98. In the population in which we investigated the diagnostic value of signs and symptoms about 10% had an AB-ratio in this range. Within this range it applies that the higher the pre-Doppler probability of PAOD — which depends on age and gender of the patient and on the results of history and physical examination performed by the doctor — the higher the AB-ratio should be to rule out disease.

Our study on the reproducibility of the AB-ratio leads to the conclusion that the Doppler method is a reproducible technique to make the diagnostic decision whether PAOD is present or not, under the condition that a 95% prediction interval of 0.15-0.20 around the measured value is taken into account. Repeated measurements should be taken to minimize the measurement variation.

We also concluded that the difference between measurements (of the same patient by the same observer) on two subsequent occasions has to be at least 0.12-0.20 to have an 80% certainty that this difference is not due to (intra-observer) measurement error. This conclusion is important if the Doppler method is used in the follow-up of patients treated for PAOD.

Measuring the AB-ratio is a skill that has to be acquired, trained and maintained.³⁰ To acquire this skill instructions by experts might be useful: experienced colleagues or practice-assistants, vascular specialists, vascular laboratory technicians. To gain

experience one will have to examine healthy and diseased legs. Initially the indication for performing the measurement will have to be taken quite liberally and half an hour should be reserved for one measurement (two arms, two legs). With growing experience the time needed for one measurement decreases to 10-15 minutes. Optimum reproducibility and accuracy will be achieved if one person in a practice (e.g. the practice assistant) performs all AB-ratio measurements.

Vascular function laboratory

In what situations is referral to a vascular function laboratory appropriate? Dutch vascular specialists recently described three situations that would be relevant. In a patient with a clinical picture suspect for PAOD but with a normal AB-ratio, a reactive hyperaemia test is suitable. If in a similar situation also information on musculoskeletal or cardiopulmonary functioning is needed, a (standardized) walking test is appropriate. Finally, if the measurement of the AB-ratio yields an inaccurate result, e.g. a very high AB-ratio in case of mediasclerosis, measurement of the toe systolic pressure is required.³¹

Referral to a vascular surgeon is necessary in case of disabling or progressive complaints. On the basis of the results of duplex-scanning he often can make a decision on the most suitable option for treatment: conservative therapy, percutaneous transluminal angioplasty or vascular surgery.³¹

MANAGEMENT OF ATHEROSCLEROSIS

Our prevalence study confirmed the findings of others that the prevalence of PAOD is higher among patients with hypertension, hypercholesterolaemia, diabetes mellitus or a history of smoking, i.e. high risk groups identifiable to the general practitioner. In accordance with others we found that compared to subjects without PAOD, both symptomatic and asymptomatic PAOD correlate with a higher probability of concomitant ischemic heart disease and cerebrovascular disease.^{7,9,32}

We confirmed the hypothesis that many cases of PAOD are unknown in primary care. *Figure 11.3* presents our results recalculated for an average Dutch solo-practice with a gender and age distribution standardized according to the Dutch population. Our data showed that the general practitioner is fairly successful in selecting the worst cases of atherosclerosis for treatment. Our results also demonstrate that efforts still can be made to improve secondary prevention.

Firstly, PAOD should be regarded as a manifestation of a systemic disease, atherosclerosis, not only in theory but also in practice. General practitioners could try to achieve a complete picture of the vascular risk profile of their middle-aged patients. In our view increased cardiovascular risk is a legitimate reason to perform a physical examination, if necessary followed by (repeated) measurement of the AB-ratio. This is illustrated in *figure 11.4*, presenting the possible outcomes of a physical examination performed in patients without complaints of intermittent claudication but with increased cardiovascular risk.

A positive outcome can be an additional motive to give lifestyle advice (smoking, exercise) to this category of patients.^{30,33} In addition, it can enhance the patient's motivation to comply with such advices. The question whether this approach indeed would be effective in reducing the number of cardiovascular events should be answered by prospective studies.

Figure 11.3 Known and unknown cases of PAOD in a standard general practice (based on the results of the prevalence study described in chapter 9)

Furthermore, in order to reduce the number of ‘unknown’ cases of PAOD, the general practitioner could more often consider the possibility of PAOD in female patients with leg complaints. Finally, a Doppler examination is appropriate when taking a careful history and performing a vascular physical examination in a patient with leg complaints yield ambiguous results.

CONCLUSIONS

In many cases the general practitioner can reject or confirm the hypothesis that PAOD is present, on the basis of medical history, physical examination and vascular risk profile. If this is not possible, he can measure the AB-ratio to reduce his diagnostic uncertainty.

Along with the clinical guidelines on the management of PAOD, published by the Dutch College of General Practitioners (‘NHG-standaard’) and the ‘Consensus’ on noninvasive diagnostic methods mentioned above, the present thesis provides a basis for good agreements between general practitioners, vascular function departments and vascular specialists.^{29,31,34-36}

The notion that PAOD is a manifestation of systemic atherosclerosis should have practical implications for the general practitioner. He still can optimize his performance with regard to the secondary prevention of cardiovascular disease. In our view casefinding among high-risk patients is a tenable option.

Figure 11.4 Predicted probability of PAOD (%) in patients without complaints of intermittent claudication but with increased cardiovascular risk depending on the outcome of a vascular physical examination

Future research

PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

The present dataset

The dataset described in this book offers various opportunities for interesting analyses in the near future.

Essential to epidemiologic studies of PAOD is the use of clear criteria and definitions when describing patients with any form of PAOD (claudication, criteria for noninvasive testing).²⁸ During their work on the Edinburgh Artery Study, *Leng and Fowkes* and co-workers tried to improve (the sensitivity of) the WHO/Rose-questionnaire on claudication.²³ An 'external' validation of their questionnaire is possible using their criteria for intermittent claudication on our dataset and comparing them to noninvasive testing.

In the prevalence study we observed that although the frequency of signs and symptoms associated with PAOD were similar for men and women, general practitioners more often diagnosed 'PAOD' among men. It would be worthwhile to do a multiple logistic regression analysis of signs, symptoms and data from the patient record using the general practitioner's diagnosis as outcome variable. This would reveal those factors which general practitioners consider important in the diagnosis of PAOD. A separate analysis for men and women would reveal whether the general practitioner's clinical judgement is different in men and women.

Future studies

To pass a definitive judgement on the value of the measurement of the AB-ratio for the general practitioner, it would be worthwhile to study the effect of the use of the Doppler device in primary care on the quantity, quality and outcome of referrals to the vascular specialist (less referrals? less diagnostic referrals and more therapeutic referrals? more PTA and less vascular surgery?).

Little is known of the effects of PAOD on the quality of life of the elderly population.¹⁵ As it was not the main focus of attention in our study, we addressed this subject only superficially in our questionnaire and did not yet analyze these data. In future studies adequate clinimetric scales to assess the quality of life of claudicants are required.²⁸ The 'PAD Walking Impairment Questionnaire' might serve this goal.^{37,38}

The Limburg PAOD study, part II

In the second part of the Limburg PAOD Study the effect of a platelet-inhibitor on the course of PAOD was investigated, using the design of a randomized controlled trial. Three hundred and eight patients were randomly assigned to one of the following groups: no intervention (natural course), calciumcarbasalate (platelet-inhibitor), placebo. All patients were instructed to stop smoking and walk daily. They were re-examined every four months during 2,5 years by their own general practitioners. Also a second study on the reproducibility of the AB-ratio was performed, using random-zero sphygmomanometers. The results of these studies will be published in the near future.

The Limburg PAOD study, part III

There still are gaps in our knowledge of the natural course of PAOD and the factors that determine its outcome.¹⁵ Early in 1994 we started to prepare a follow-up study of patients that were examined during the years 1987-1990.³⁹ Goal of this third Limburg PAOD Study is to investigate the incidence of PAOD and to assess prognostic determinants for the disease. We hope to find those signs, symptoms and risk factors for PAOD that have prognostic value for the course of the disease, i.e. factors that can discriminate between those patients who are at high risk for progression to critical limb ischemia or for the occurrence of other atherosclerotic disease, and those patients who are not. From a preventive perspective we have a particular interest in the fate of formerly asymptomatic PAOD cases.

Criteria and codes for PAOD

If general practice morbidity registration systems are to be used as epidemiological databases, a clear definition of codes is necessary. In this connection it should be noticed that the current codes for PAOD in the International Classification of Primary Care (ICPC) impede epidemiologic research in general practice.⁴⁰ Intermittent claudication can be coded K03 (pain attributed to circulation) and K92 (other arterial obstructions, peripheral vascular disease). In fact code K91 (atherosclerosis excluding heart/brain) would be more appropriate. This is a confusing situation.

In our view 'intermittent claudication' should be regarded as a complaint that is associated with PAOD but is not identical to PAOD. Therefore, if no other data are available, code K03 would be appropriate, with a sub-code to distinguish it from complaints normally associated with venous insufficiency. If more clinical data are available (physical examination, risk factors, AB-ratio, extensive noninvasive testing, a history of PTA, vascular surgery or amputation) code K91 would be suitable. Sub-codes could be given to indicate the severity of the disease. Code K92 could be reserved for non-atherosclerotic peripheral vascular diseases (Bürger's disease, Raynaud's disease).

DIAGNOSTIC RESEARCH

Multivariable analysis of diagnostic associations is not a textbook procedure yet.^{41,42} Few examples to learn from were available.⁴³⁻⁴⁵ Using multiple logistic regression to analyze the diagnostic value of clinical data, some conceptual inconveniences were encountered.

In order to approach the normal clinical diagnostic work up, we had to ensure a hierarchical order of our successive models. Therefore the sequence of variable clusters was input of the analysis, not outcome of the model. Changing the combination of variables, e.g. by varying the sequence of entering clusters of terms, implies a change of the coefficient i.e. the odds ratio of a variable. In contrast to the 'adjusted odds ratio' in etiologic studies — being the true (= unconfounded) measure of the independent contribution of a risk factor to the outcome of interest — the multivariable diagnostic odds ratio should be interpreted as a measure of the relative contribution of a specific diagnostic test given a certain combination of tests. Intuitively, one is inclined to regard upon the bivariate diagnostic odds ratio as the 'true' estimate of the diagnostic value of this particular test for the outcome

of interest (i.e. a particular diagnosis).

The presence of collinearity in some clusters of variables forced us to skip variables from the models (e.g. 'femoral pulse') or to combine variables into a new compound variable (e.g. 'dorsalis pedis pulse: no-weak-yes' and 'posterior tibial pulse: no-weak-yes' were combined to 'pedal pulses: abnormal-doubt-normal'). From a clinical point of view this felt rather artificial.

An alternative approach to the analysis of diagnostic data was suggested by *Knottnerus*.⁴⁶ After discussing the limitations of conventional multiple logistic regression for this purpose, he proposes a method based on a particular transformation of test variables, a simple branching structure and a sequence of entering terms in decreasing order of gain in certainty. This approach takes account of the fact that the next step in a diagnostic work up is dependent on the outcome of the previous step. Another benefit of this method would be that entering or skipping variables does not affect coefficients previously included in the model. A computer programme using this method is currently being developed. We intend to analyze our data using this alternative analysis method.

EPIDEMIOLOGIC RESEARCH AND MORBIDITY REGISTRATION IN (DUTCH) GENERAL PRACTICE

Having completed this part of the Limburg PAOD study, the question can be raised: are large scale population studies the most efficient way to study the descriptive and clinical epidemiology of chronic diseases the general practitioner has to deal with? Should clinical research in general practice not be done by its natural investigators, the general practitioner and his practice assistant, in its natural surroundings, the general practitioner's office?

Every day general practitioners collect data on the incidence and clinical diagnosis of diseases, the prevalence of manifest disease, the course of chronic diseases, treatment strategies and the relationship between disease and social context. The work of *Lamberts et al.* shows how — even in the pre-computer era — basic clinical data describing the 'transition' from reason for encounter via diagnosis to treatment, can be used to create a research based textbook of general practice.⁴⁷

However, clinical data recorded in the average general practice do not meet criteria for validity and precision to be expected from research data, like the use of clear and consistent definitions, completeness of patient records, and the independent assessment of predictor and outcome variables. Therefore, — as was the case with our study — collecting research data in general practice often is done according to a special research protocol that interferes more or less with normal patient care activities.⁴⁸

The extent of computerization among (Dutch) general practitioners is increasing. Personal computers are used not only for the financial administration but also for keeping electronic medical records. *Höppener* concluded that collecting research data 'at the source' i.e. in the general practitioner's office, still is the stepchild of practice computerization. He and his colleagues showed that it can be done.⁴⁹ The growth of practice computerization has facilitated the development of general practice morbidity registration networks.⁵⁰ *Metsemakers et al.* have demonstrated how data of a computerized registration network can be used for research, medical education and quality assurance.⁵⁰

Doctors involved in morbidity registration will get used to coding according to well defined criteria. Doctors involved in quality assurance and practice audit will get used to working with clinical guidelines and protocols. General practice guidelines based on general practice research, systematic literature reviews and consensus-procedures, are increasingly becoming available. A positive effect of these trends could be a growing interest and willingness among general practitioners to record clinical data in a complete ('according to protocol') and accurate ('according to criteria') fashion.

To facilitate these processes computerized clinical protocols (on diagnostic management, on monitoring the course of a disease, on functional status etcetera) will have to be developed. Only if these programmes can easily be integrated in the daily routine of the general practitioner, the electronic medical record can transform into a medical database to be used in medical education, research and practice audit.⁵¹

With regard to diagnostic research the advantage of computerized practice based data collection would be a controlled and realistic selection of patients for whom a (new) diagnostic test would be appropriate ('indicated' or 'clinically relevant' population). Also the issue of the 'gold standard' could be solved in some cases by watchful waiting for a disease to develop to a clear, predefined condition ('pseudo follow-up study'). E.g. the diagnostic programme for PAOD currently being developed on the basis of our multivariable diagnostic models ('LIMB', 9 items, available from the author) could be used to facilitate a study to validate our models in an indicated population. In such a study the outcome of repeated AB-ratio measurements could serve as a gold standard.

CONCLUSIONS

Data on the conservative treatment of PAOD, prognostic indicators and the relevance of asymptomatic PAOD will become available in the next years. The alternative approach to the analysis of diagnostic data proposed by *Knottnerus*, can be tested using our data set.

It would be worthwhile to study the effect of the use of the Doppler device in primary care on the quantity, quality and outcome of referrals to the vascular specialist. Also, more studies on the quality of life in PAOD patients are required.

Practice based epidemiologic research of chronic diseases is possible only if everyday clinical data are collected according to research standards. Practice based research on PAOD requires above all consistent definitions (e.g. on intermittent claudication) and codes (ICPC!) for PAOD. Practice based data collection will be facilitated when computerized protocols that easily can be integrated in the daily routine of the general practitioner will become available.

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Chapter 12 Summary

This thesis describes studies on the prevalence and diagnostic management of peripheral arterial occlusive disease (PAOD) in general practice. PAOD refers to the manifestation of atherosclerosis in the lower limb distal to the aortic bifurcation.

There is a number of reasons for paying attention to the management of patients with PAOD in general practice: diagnosis, conservative treatment and monitoring of patients with this chronic disorder are primarily tasks of the general practitioner; the disease may lead to serious complications that should be prevented wherever possible; PAOD is an expression of generalized atherosclerosis; therefore, regular monitoring of risk indicators for cardiovascular disease might be appropriate in PAOD patients.

Chapter 2 presents a literature review on PAOD. The emphasis lies with data regarding the prevalence and the diagnosis of the disease. Literature was gathered systematically from the MEDLINE database and by using the 'snowball method'. This chapter represents the state of affairs known to us in March 1990.

The reported prevalence of PAOD ranges from 0.2 to 11.7%. It is plausible that many patients will not be known to the general practitioner and that there will be a large category of asymptomatic patients.

The prognosis of intermittent claudication is reported to be relatively favourable: in only about a quarter of patients symptoms progress. However, the prognosis *quod vitam* of patients with intermittent claudication is rather poor, due to the greatly increased risk of the development of cardiovascular and cerebrovascular complications. Possibly this applies to asymptomatic patients as well.

Little research has been done on the diagnostic significance of signs and symptoms associated with PAOD. From the available data it may be concluded that the current clinical diagnostic methods permit the general practitioner to exclude PAOD, whereas establishing the diagnosis cannot be done with sufficient certainty. Only few data on the diagnostic value of combinations of signs and symptoms are available.

In this respect the measurement of the resting ankle-brachial systolic pressure ratio (AB-ratio) by means of a pocket Doppler device — a noninvasive technique used for diagnosing PAOD — could be an asset to general practice. In *chapter 3* the literature on the reproducibility and the validity of this method is examined. In addition the merits of the pocket Doppler device are compared to the possibilities of a vascular laboratory. Literature was gathered systematically from the MEDLINE database and by using the 'snowball method'. This chapter represents the state of affairs known to us in March 1990.

The reproducibility of the AB-ratio measurement is reported to be acceptable: the

95% prediction interval around a measured value is ± 0.14 to ± 0.20 .

Using the resting AB-ratio, it appears well feasible to differentiate between angiographically 'nondiseased' and 'occluded' arteries. The distinction between 'nondiseased' and 'stenosed' vessels seems less clear.

The selection of a cutoff value for the AB-ratio in the 0.90 to 1.00 range is open to discussion. In the most valid studies sensitivity varies between 75 and 97% and specificity between 92 and 100% at a cutoff point of 0.90. Using a cutoff value of 1.00, sensitivity varies between 88 and 100% and specificity varies between 60 and 80%. Pooling the results of four comparable studies yields 82% for mean sensitivity and 98% for mean specificity at the cutoff value of 0.90. Using a cutoff value of 1.00 these figures are 88% and 81% respectively.

The vascular laboratory is able to offer diagnostic information that is harder and more comprehensive than the pocket Doppler measurements. However, applying the pocket Doppler device in general practice may lead to a more selective management with regard to treatment and referral.

In *chapter 4* the main objectives of the study are described. We wanted to answer the following questions:

- 1 What is the prevalence of PAOD in the general practice population?
- 2 What is the diagnostic significance of signs and symptoms in PAOD?

In addition we wanted to study the following issues:

- The reproducibility of the measurement of the ankle-brachial systolic pressure ratio.
- The diagnostic power of the measurement of the ankle-brachial systolic pressure ratio.

Chapter 5 discusses the general design, methods and variables of the main study on the prevalence and clinical diagnosis of PAOD. The definitive study population was recruited from a population consisting of the male and female patients — born between 1 November 1911 and 31 December 1946, on the list of 18 general practice centres — by means of a postal questionnaire on complaints and risk factors (yielding a 'prior risk score' ranging from zero to five), followed by a sampling and selection procedure.

Data collection in the general practice centres occurred according to a cross-sectional design and consisted of two parts which had to be executed independently:

- 1 data from the medical history were provided by the patient in a questionnaire, and data on findings of the physical examination, previous medical history, medication, co-morbidity and diagnosis were collected by the general practitioner.
- 2 the measurement of the AB-ratio by means of a pocket Doppler device was carried out by a practice assistant. This 'Doppler measurement' was used as standard diagnostic test. Patients with an AB-ratio lower than 0.95 on two consecutive occasions (interval: one week) were considered to have PAOD.

All the anonymous and coded variables described in this chapter were read into the university's mainframe computer. Personal details of the patients were stored separately in a database on a personal computer.

Chapter 6 presents a quantitative overview of the processes of selection and drop-out that led to the definitive study population. The extent of selective drop-out is

assessed. Finally, the study population is described for a number of key parameters.

The source population consisted of 26620 patients with a mean age of 56.5 years (range: 40.3-76.9 years) of whom 52.5% were female. The overall response on the postal questionnaire was 86.4%. The average response rate per practice was 85.7% (SD: 3.4%). The non-response did not cause a significant selective drop-out by age or gender.

There were 9095 responders with a prior risk score of zero and 13909 responders with a score from one to five. From the population of responders two random samples were taken: from the category with a score of zero (group 1, 'no risk', n=451) and from the category with a score of one to five (group 2, 'increased risk', n=897). Both samples proved to be representative for their respective source populations with regard to age and gender. Of the remaining patients with a score between one and five, those at highest risk were selected (group 3, 'high risk', n=3953).

Thus, 5301 subjects were invited for an examination in one of the 18 general practice centres. The invitation was accepted by 68.9%. The average participation rate per practice was 70.2% (SD: 11.9%). Non-participation was due to various reasons: patients stayed in hospital for a protracted period or had moved or had died (17.5%); many patients were 'not interested' (48%); sometimes general practitioners decided that a patient would not participate for medical or practical reasons (11%). The remaining causes for non-participation were unknown (23.5%). The non-participation was selective to a certain degree for 'age' (older age groups), 'gender' (males), and 'score' (inconsistent pattern).

The definitive study population comprised 3654 patients (group 1: 292; group 2: 626; group 3: 2736) aged 40.7-78.3 years (mean age: 59.1 years), of whom 53.0% were female.

Since we intended to use the measurement of AB-ratio by means of a hand held Doppler device as 'standard' diagnostic test, we performed additional studies on the reproducibility and validity of this method for general practice.

In *chapter 7* the results of our study on the reproducibility of the measurement of the AB-ratio are described. The magnitude of different sources of measurement variation, relevant to clinical practice as well as multi-observer studies, was estimated from a random effects analysis of variance model. Thirty-five general practitioners and 24 practice assistants performed 503 AB-ratio measurements on nine patients over a period of nine weeks, using pocket Doppler devices.

When the AB-ratio is used for diagnostic purposes, a 95% prediction interval consisting of the measured value ± 0.15 - 0.20 has to be taken into account. Furthermore, when the AB-ratio is used in the follow-up of a patient with vascular disease, the difference between two subsequent measurements has to be at least 0.16 - 0.19 to have an 80% certainty that this difference is not due to (intra-observer) measurement error.

In conclusion, the measurement of the AB-ratio is a reproducible technique under the condition that a 95% prediction interval of 0.15 - 0.20 around the measured value is taken into account. Repeated measurements should be taken to minimize the measurement variation.

In *Chapter 8* our study on the diagnostic power of the measurement of the AB-ratio

is described. We assessed the accuracy and diagnostic value of the AB-ratio, estimated the optimum cutoff value for the AB-ratio and estimated threshold cutoff values beyond which PAOD can be ruled in or out. The diagnostic outcome of the measurement of the AB-ratio in three general practice centres was compared to the diagnostic conclusions of a Vascular Laboratory. This was done for the outcome of single AB-ratio measurements (231 legs of 117 patients) and the outcome of measurements on three consecutive occasions (subgroup of 92 legs of 51 patients).

Receiver Operating Characteristic (ROC) analysis showed that the diagnostic value of the mean of three AB-ratios is better than that of a single AB-ratio. The best theoretical optimum cutoff value was a mean AB-ratio of 0.92 (sensitivity 87%, specificity 91%, likelihood ratio of a positive test 10, likelihood ratio of a negative test 0.14). Accuracy, corrected for prevalence, was 90%.

We estimated that the positive predictive value $\geq 95\%$ if the mean of three consecutive AB-ratios is below 0.88; the negative predictive value $\geq 99\%$ if the mean AB-ratio is above 0.98 (prevalence range 5-33%).

We concluded that the measurement of the AB-ratio with a hand-held Doppler device is a valid diagnostic method for general practice. To maximize diagnostic performance one ought to measure the AB-ratio on more than one occasion before reaching a definite diagnostic conclusion.

Chapter 9 presents our study on the prevalence of peripheral arterial occlusive disease. The prevalence of PAOD, including asymptomatic cases and cases unknown to the general practitioner, was estimated in 18884 patients, aged 45-75 years, on the list of 18 general practice centres.

The study population ($n=3171$) consisted of a sample of the total population. In the general practice centres data were collected on intermittent claudication (IC), peripheral pulses, vascular risk factors, cardio- and cerebrovascular disease and the AB-ratio. PAOD was defined as an AB-ratio < 0.95 on two consecutive occasions. Results were recalculated for the total population.

The prevalence of PAOD was 6.9% (95%ci 5.7-8.2%). One third of all cases (2.2%) had an AB-ratio < 0.75 . The prevalence of IC was 6.6% (95%ci 5.2-7.9%), of which a quarter (1.6%) met the classic WHO-criteria. The prevalence of abnormal pedal pulses was 8% (95%ci 6.5-9.5%). PAOD did not occur significantly more often among men than among women but men more often suffered from an advanced stage of PAOD. Of all cases of PAOD 22% was symptomatic. This proportion correlated positively with higher age, male gender and lower AB-ratio. Among asymptomatic PAOD cases the prevalence of concomitant cardio- and cerebrovascular disease was three to four times as high as in the group without PAOD. Sixty-eight % of all PAOD cases was unknown to the general practitioner. This 'unknown' group mainly represented less advanced cases of atherosclerosis. Still, of the group of PAOD cases with an AB-ratio < 0.75 , 42% was unknown to the general practitioner.

We concluded that general practitioners succeed in selecting the worst cases of manifest atherosclerosis but can enhance their efforts towards secondary prevention.

In *chapter 10* the our study on the diagnostic value of signs and symptoms associated with PAOD is presented. We compared clinical data on PAOD — collected in 18 general practice centres (1340 women, 1115 men, age 40.7-78.4 years) — to the

outcome of the measurement of the AB-ratio. PAOD was considered to be present if the AB-ratio was below 0.95 on two consecutive occasions (11.5% of all legs). Data were analyzed using multiple logistic regression analysis.

Three classic features of PAOD appeared to be the most informative diagnostic tests: questioning the patient for intermittent claudication (bivariate diagnostic odds ratio 5.5, sensitivity 28%, specificity 93%), palpation of both foot pulses (odds ratio 22.7, sensitivity 66%, specificity 80-92%, best single diagnostic procedure) and auscultation of the femoral artery (odds ratio 7.7, sensitivity 27%, specificity 95%). The multivariable odds ratios of these variables were 3.3, 12.8 and 4.1 respectively.

Data like gender (odds ratio 1.3), age above 60 (odds ratio 2.2), unilateral lower skin temperature (odds ratio 2.1), high blood pressure (odds ratio 1.5), a history of smoking (odds ratio 2.2) or the presence of coronary artery disease (odds ratio 1.8) can also significantly contribute to the probability of PAOD. This is particularly relevant in cases that do not represent the classic clinical picture.

Our multivariable diagnostic models support the intuitive estimate of the probability of PAOD the general practitioner will have after each stage of his clinical evaluation of the patient. In many patients he will be able to rule out disease with a high degree of certainty (60% of all legs in our study population had a predicted probability of PAOD < 0.05). In a small group of patients he can reach a high degree of certainty that PAOD is present (1.3% of all legs in our study population had a predicted probability of PAOD > 0.80). If the probability of PAOD is not low enough to exclude disease but not high enough to establish the diagnosis PAOD (in our study population 38% of all legs had a predicted probability of PAOD between 0.05 and 0.80), the general practitioner might consider noninvasive testing to resolve his diagnostic uncertainty.

In conclusion, it would be useful to realize an external validation of our models by testing their performance in a similar study population. Our current analysis indicated that traditional clinical evaluation enables the general practitioner to decide upon the need for further diagnostic or therapeutic action in patients suspected of having PAOD.

In *chapter 11* the main results of this study are discussed in relation to our objectives and the literature. Also various methodological issues are summarized, the implications of our results for general practice are formulated and some ideas on future research in this field are presented.

The present study demonstrates that in many cases the general practitioner can reject or confirm the hypothesis that PAOD is present, on the basis of medical history, physical examination and the vascular risk profile of a patient.

If this is not possible, the general practitioner can use the hand held Doppler device for measuring the AB-ratio, a valid and reproducible supplementary test, to reduce his diagnostic uncertainty. Practical decision rules for the measurement and interpretation of the AB-ratio are provided. The results of the present study can contribute to good agreements between general practitioners, vascular function departments and vascular specialists, on the use of noninvasive diagnostic techniques for PAOD.

The notion that PAOD is a manifestation of systemic atherosclerosis should have practical implications for the general practitioner. This study shows that there are possibilities for the general practitioner to optimize his performance with regard to

the secondary prevention of cardiovascular disease.

In the near future we hope to publish results on the conservative treatment of PAOD, prognostic indicators and the relevance of asymptomatic disease. An alternative approach to the analysis of diagnostic data could be tested using our data set.

More studies on the quality of life in PAOD patients are required. It would also be worthwhile to study the effect of the use of the Doppler device in primary care on the quantity, quality and outcome of referrals to the vascular specialist.

Above all, practice based research on PAOD requires consistent definitions and codes for PAOD. In general, practice based epidemiologic research of chronic diseases is possible only if everyday clinical data are collected according to research standards. This will be facilitated when computerized protocols that easily can be integrated in the daily routine of the general practitioner will become available.

Chapter 13 Samenvatting

In dit boek wordt een onderzoek naar de prevalentie en de diagnostiek van perifeer arterieel obstructief vaatlijden (PAV, perifeer arterieel vaatlijden) in de huisartspraktijk beschreven. Met 'perifeer arterieel obstructief vaatlijden' bedoelen we arterieel vaatlijden distaal van de bifurcatie van de aorta veroorzaakt door atherosclerose.

Hoofdstuk 1 bevat de inleiding. Om een aantal redenen verdient perifeer arterieel vaatlijden de aandacht van de huisarts: diagnostiek, conservatieve behandeling en het blijven volgen van patiënten met deze chronische aandoening zijn primair taken van de huisarts; de ziekte kan leiden tot ernstige complicaties die zo goed mogelijk voorkómen dienen te worden; perifeer arterieel vaatlijden is een manifestatie van gegeneraliseerd arterieel vaatlijden, hetgeen regelmatige controle van risicofactoren voor hart- en vaatziekten wenselijk maakt.

In *hoofdstuk 2* geven we een overzicht van de literatuur over perifeer arterieel vaatlijden voor zover relevant voor de huisartsgeneeskunde. De nadruk ligt bij gegevens over de prevalentie en de diagnostiek van de aandoening. Literatuur werd systematisch verzameld via het MEDLINE databestand. Tevens werd de 'sneeuwbal-methode' gebruikt. Dit hoofdstuk geeft de stand van zaken weer van maart 1990.

De in de literatuur gerapporteerde prevalentie van perifeer arterieel vaatlijden varieert tussen 0.2 en 11.7%, waarbij het aannemelijk is dat veel patiënten niet als zodanig bij de huisarts bekend zijn en dat de categorie patiënten zonder klachten ('asymptomatische gevallen') groot is.

De prognose van claudicatio intermittens als zodanig, wordt als relatief gunstig beschreven: slechts in een kwart van de gevallen zouden symptomen verergeren. De prognose *quod vitam* van patiënten met claudicatio intermittens is relatief slecht, ten gevolge van een verhoogd risico op het ontwikkelen van manifest hart- en hersen-vaatlijden. Dit verhoogde risico geldt mogelijk ook voor mensen met asymptomatisch perifeer arterieel vaatlijden.

Er blijkt weinig onderzoek gedaan te zijn naar de diagnostische waarde van anamnese en lichamelijk onderzoek. Op basis van de gegevens uit de literatuur kan geconcludeerd worden dat de huisarts met de gangbare klinisch-diagnostische methoden perifeer arterieel vaatlijden goed kan uitsluiten, maar dat de diagnose veel minder zeker gesteld kan worden. Er is echter nauwelijks informatie voorhanden over de diagnostische waarde van gecombineerde gegevens uit anamnese en lichamelijk onderzoek.

In dit opzicht zou de bepaling van de enkel-arm-index (EA-index) in rust, met behulp van een pocket-Doppler-apparaat, een aanwinst kunnen zijn voor de huisartspraktijk. In *hoofdstuk 3* wordt de literatuur over de reproduceerbaarheid en

de validiteit van deze methode besproken. Bovendien worden de mogelijkheden van het pocket-Doppler-apparaat vergeleken met de mogelijkheden die een vaatlaboratorium biedt. Literatuur werd systematisch verzameld via het MEDLINE databestand. Ook dit hoofdstuk geeft de stand van zaken weer van maart 1990.

Uit de literatuur blijkt dat de reproduceerbaarheid van de bepaling van de EA-index acceptabel is: het 95%-voorspellingsinterval rond een gemeten waarde bedraagt ± 0.14 tot ± 0.20 .

Verder blijkt het goed mogelijk om met behulp van de EA-index een onderscheid te maken tussen angiografisch 'gezonde vaten' en 'vaten met occlusies'. Het onderscheid tussen 'gezonde vaten' en 'vaten met stenosen' is minder scherp te trekken.

Omtrent de keuze van een afkappunt voor de EA-index, ergens in het gebied tussen 0.90 en 1.00, blijkt geen consensus te bestaan. De meest valide onderzoeken vinden bij een afkappunt van 0.90 een sensitiviteit variërend van 75 tot 100% en een specificiteit variërend van 80 tot 100%. Bij een afkappunt van 1.0 varieert de sensitiviteit tussen 88 en 100% en de specificiteit tussen 60 en 80%. Indien de gegevens van methodologisch vergelijkbare studies gepoold worden, bedraagt de gewogen gemiddelde sensitiviteit 82% en de gewogen gemiddelde specificiteit 98% bij een afkappunt van 0.90; deze cijfers zijn 88% respectievelijk 81% bij een afkappunt van 1.0.

Het vaatlaboratorium biedt diagnostische gegevens die harder en meer omvattend zijn dan de bepaling van de EA-index. Toch zou toepassing van de pocket-Doppler in de huisartspraktijk kunnen leiden tot een meer selectief behandel- en verwijzbeleid.

In *hoofdstuk 4* komen de vraagstellingen van dit onderzoek aan de orde. We wilden de volgende vragen beantwoorden:

- 1 Wat is de prevalentie van perifeer arterieel vaatlijden in een huisartsgeneeskundige populatie?
- 2 Wat is de diagnostische waarde van gegevens uit anamnese en lichamelijk onderzoek bij perifeer arterieel vaatlijden?

Daarnaast wilden we de volgende onderwerpen bestuderen:

- De reproduceerbaarheid van de bepaling van de EA-index.
- De diagnostische waarde van de bepaling van de EA-index.

In *hoofdstuk 5* behandelen we de algemene opzet, methodologie en variabelen van het (hoofd-)onderzoek naar de prevalentie en de klinische diagnostiek bij perifeer arterieel vaatlijden. De uiteindelijke onderzoekspopulatie werd geselecteerd door middel van een post-enquête uit de populatie patiënten, geboren tussen 1 november 1911 en 31 december 1946, van 18 huisartspraktijken. Na beantwoording van de post-enquête (5 vragen over klachten en risicofactoren) kon aan iedere patiënt een 'a priori risico-score' (kortweg 'score') worden toegekend; op grond hiervan werd de uiteindelijke onderzoekspopulatie geselecteerd.

De gegevensverzameling in de huisartspraktijken verliep volgens een dwarsdoorsnede-opzet en bestond uit twee onderdelen die onafhankelijk van elkaar dienden plaats te vinden:

- 1 anamnestiche gegevens werden verzameld door de patiënt een vragenlijst te laten invullen; gegevens met betrekking tot het lichamelijk onderzoek, medische

voorgeschiedenis, medicatie-gebruik, co-morbiditeit en diagnose werden door de huisarts geleverd;

- 2 de bepaling van de EA-index met behulp van een pocket-Doppler apparaat werd bij voorkeur door de praktijkassistente uitgevoerd. Deze 'Dopplerbepaling' werd gebruikt als standaard-diagnosticum. Patiënten met een EA-index lager dan 0.95 bij twee opeenvolgende gelegenheden (interval: 1 week) werden beschouwd als patiënt met perifere arterieel vaatlijden.

Alle gegevens werden anoniem en gecodeerd ingevoerd in de mainframe-computer van de Rijksuniversiteit Limburg. Personalia van patiënten werden apart opgeslagen in een gegevensbestand op een personal computer.

In *hoofdstuk 6* geven we een kwantitatief overzicht van het proces van selectie en uitval, dat uiteindelijk de samenstelling van de onderzoekspopulatie bepaalde.

De bron-populatie bestond uit 26620 patiënten, waarvan 52.5% vrouw was en waarvan de leeftijd varieerde van 40.3 tot 76.9 jaar (gemiddeld 56.5 jaar). De mate van respons op de post-enquête was 86.4%. De gemiddelde respons per praktijk bedroeg 85.7% (SD: 3.4%). De non-respons veroorzaakte geen selectieve uitval met betrekking tot geslacht en leeftijd.

Er waren 9095 respondenten met een 'score' van nul en 13909 respondenten met een 'score' variërend tussen 1 en 5. Uit de populatie respondenten werden twee steekproeven getrokken: uit de categorie met een 'score' van 0 (groep 1, 'geen risico', $n=451$) en uit de categorie met een 'score' tussen 1 en 5 (groep 2, 'verhoogd risico', $n=897$). Beide steekproeven bleken representatief voor hun respectievelijke bron-populaties met betrekking tot leeftijd en geslacht. Van de overblijvende patiënten met een 'score' tussen 1 en 5, werden diegenen met de hoogste score geselecteerd (groep 3, 'hoogste risico', $n=3953$).

Aldus werden 5301 mensen uitgenodigd voor een onderzoek in de praktijk van hun eigen huisarts. Deze uitnodiging werd aangenomen door 68.9% van de patiënten. Het gemiddelde participatie-percentages per praktijk bedroeg 70.2% (SD: 11.9%). Patiënten deden niet mee om diverse redenen: een aantal patiënten was inmiddels gestorven, verhuisd, of langdurig opgenomen in ziekenhuis, psychiatrisch centrum of verpleeghuis (17.5% van de uitvallers); een grote groep patiënten gaf aan 'niet geïnteresseerd' te zijn (48%); soms besloot de huisarts dat een patiënt niet mee zou doen aan het onderzoek vanwege medische of praktische redenen (11%). In de resterende gevallen bleef de reden van non-participatie onbekend (23.5%).

Tot op zekere hoogte was de uitval selectief met betrekking tot 'leeftijd' (oudere leeftijdsgroep), 'geslacht' (mannen) en 'score' (wisselend patroon). De uiteindelijke onderzoekspopulatie bestond uit 3654 patiënten (groep 1: 292; groep 2: 626; groep 3: 2736) met een leeftijd variërend van 40.7 tot 78.3 jaar (gemiddeld: 59.1 jaar), waarvan 53% vrouw was.

Aangezien we van plan waren de bepaling van de EA-index met een hand-Doppler-apparaat als 'standaard-diagnosticum' te gebruiken, verrichtten we onderzoek naar de reproduceerbaarheid en de validiteit van deze methode voor de huisartspraktijk.

In *hoofdstuk 7* worden de resultaten van ons onderzoek naar de reproduceerbaarheid van de bepaling van de EA-index beschreven. Vijfendertig huisartsen en 24 praktijkassistenten voerden 503 EA-index-bepalingen uit met een hand-Doppler bij 9 patiënten in een periode van 9 weken. Het aandeel van verschillende bronnen van

meetvariabiliteit, van belang voor de huisartspraktijk en voor epidemiologisch onderzoek, werd geschat door middel van een 'random effects analysis of variance'-model.

We vonden dat als de EA-index gebruikt wordt met een diagnostisch doel, er rekening gehouden dient te worden met een 95% voorspellingsinterval rond de gemeten waarde van ± 0.135 tot ± 0.225 . Bovendien, als de EA-index gebruikt wordt bij het vervolgen van een patiënt met perifeer arterieel vaatlijden, dan dient het verschil tussen twee opeenvolgende metingen tenminste 0.16-0.19 te zijn om met 80% zekerheid te kunnen zeggen dat dit verschil niet te wijten is aan toevallige (intra-waarnemer)-meetvariatie.

We concludeerden dat de bepaling van de EA-index een reproduceerbare methode is, onder de voorwaarde dat een 95% voorspellingsinterval van ± 0.15 à 0.20 wordt aangehouden. Het herhalen van de meting bevordert de betrouwbaarheid van de uitslag.

In *hoofdstuk 8* wordt ons onderzoek van de diagnostische waarde van de bepaling van de EA-index beschreven. De diagnostische uitkomst van de EA-index-bepaling in drie gezondheidscentra werd vergeleken met de diagnostische conclusie van een vaatlaboratorium. Dit werd gedaan voor zowel enkelvoudige bepalingen van de EA-index (231 benen van 117 patiënten), als voor de uitkomst van het gemiddelde van bepalingen tijdens 3 opeenvolgende consulten (subgroep van 92 benen van 51 patiënten). We bepaalden het discriminerend vermogen en het optimale afkappunt voor de EA-index en berekenden drempelwaarden waarbij perifeer arterieel vaatlijden met zekerheid kan worden uitgesloten respectievelijk kan worden aangetoond.

'Receiver operating characteristic' (ROC) analyse liet zien dat de diagnostische waarde van het gemiddelde van 3 opeenvolgende bepalingen van de EA-index, beter is dan die van een enkelvoudige bepaling van de EA-index. Het beste theoretisch optimale afkappunt voor het gemiddelde van 3 bepalingen was 0.92 (sensitiviteit 87%, specificiteit 91%, aannemelijkheids-coëfficiënt voor een positieve testuitslag 10, aannemelijkheids-coëfficiënt voor een negatieve testuitslag 0.14). Het aantal correcte classificaties, gecorrigeerd voor prevalentie, bedroeg 90%. We berekenden dat de voorspellende waarde van een positieve testuitslag $\geq 95\%$ als het gemiddelde van 3 opeenvolgende bepalingen van de EA-index kleiner is dan 0.88; de voorspellende waarde van een negatieve testuitslag $\geq 99\%$ als de gemiddelde EA-index groter is dan 0.98 (in het prevalentiebereik 5-33%).

We concludeerden dat de bepaling van de EA-index met een pocket-Doppler-apparaat een valide diagnostische methode voor de huisartspraktijk is. Om het diagnostisch vermogen van de bepaling te maximaliseren dient men de EA-index bij meerdere gelegenheden te bepalen alvorens een diagnostische conclusie te trekken.

In *hoofdstuk 9* komt het onderzoek naar de prevalentie van perifeer arterieel vaatlijden aan de orde. Het aantal gevallen van perifeer arterieel vaatlijden, inclusief asymptomatische gevallen en gevallen die niet bij de huisarts bekend waren, werd bepaald voor een populatie van 18884 patiënten, in leeftijd variërend tussen 45 en 75 jaar, ingeschreven bij 18 huisartspraktijken.

De onderzochte populatie ($n=3171$) bestond uit een selectie van de totale populatie. In de huisartspraktijken werden gegevens verzameld met betrekking tot claudicatio intermittens (CI), perifere pulsaties, vasculaire risicofactoren, hart- en

hersenvaatlijden en de EA-index. De definitie van perifeer arterieel vaatlijden was tweemaal een EA-index < 0.95 (interval: 1 week). De resultaten werden terugerekend naar de totale populatie.

We vonden een prevalentie van perifeer arterieel vaatlijden van 6.9% (95%bi 5.7-8.2%); een derde deel van de gevallen (2.2%) had een EA-index < 0.75 . De prevalentie van CI was 6.6% (95%bi 5.2-7.9%), waarbij een vierde deel van de gevallen (1.6%) voldeed aan de klassieke WHO-criteria voor CI. De prevalentie van abnormale perifere pulsaties bedroeg 8% (95%bi; 6.5-9.5%). Perifeer arterieel vaatlijden kwam niet significant vaker voor bij mannen dan bij vrouwen, maar bij mannen was vaker sprake van een meer voortgeschreden vorm van perifeer arterieel vaatlijden. Bij een vijfde deel (22%) van alle gevallen van perifeer arterieel vaatlijden was sprake van klachten van CI ('symptomatisch'). Deze proportie correleerde met leeftijd (ouder), geslacht (man) en EA-index (lager). In de groep asymptomatische gevallen van perifeer arterieel vaatlijden was de prevalentie van eveneens aanwezig hart- of hersenvaatlijden 3 tot 4 maal zo hoog als in de groep zonder perifeer arterieel vaatlijden. Achteenzestig procent van alle gevallen van perifeer arterieel vaatlijden was niet als zodanig bij de huisarts bekend. Deze 'onbekende' groep bestond voornamelijk uit minder ernstige gevallen van perifeer arterieel vaatlijden (meer vrouwen, jonger, minder lage EA-index, minder klachten). Toch bleek in de groep patiënten met een EA-index < 0.75 , nog 42% onbekend bij de huisarts.

We concludeerden dat huisartsen erin slagen de meest ernstige gevallen van manifeste atherosclerose te selecteren voor begeleiding en behandeling, maar dat zij hun activiteiten op het gebied van secundaire preventie van hart- en vaatziekten nog kunnen aanscherpen.

In *hoofdstuk 10* wordt ons onderzoek naar de diagnostische betekenis van klachten en bevindingen bij perifeer arterieel vaatlijden besproken. Wij vergeleken klinische gegevens verzameld in 18 huisartspraktijken bij 1340 vrouwen en 1115 mannen in de leeftijd van 40.7-78.4 jaar, met de uitkomst van de bepaling van de EA-index. perifeer arterieel vaatlijden werd aanwezig geacht als de EA-index bij twee opeenvolgende gelegenheden (interval: 1 week) lager dan 0.95 was (11.5% van alle benen). De gegevens werden bivaariaat en met behulp van multiple logistische regressie geanalyseerd.

We vonden dat de drie klassieke kenmerken van perifeer arterieel vaatlijden de meest informatieve diagnostische 'testen' bleken te zijn: het afnemen van een anamnese naar claudicatio intermittens (bivariate diagnostische odds ratio 5.5, sensitiviteit 28%, specificiteit 93%), palpatie van beide voetarteriën (odds ratio 22.7, sensitiviteit 66%, specificiteit 80-92%, beste enkelvoudige diagnostische procedure) en auscultatie van de arteria femoralis (odds ratio 7.7, sensitiviteit 27%, specificiteit 95%). De multivariabele odds ratio's van deze variabelen waren respectievelijk 3.3, 12.8 en 4.1.

Echter ook andere kenmerken kunnen bijdragen tot een verhoogde kans op perifeer arterieel vaatlijden: mannelijk geslacht (odds ratio 1.3), leeftijd boven de 60 (odds ratio 2.2), eenzijdig koudere huidtemperatuur (odds ratio 2.1), hoge bloeddruk (odds ratio 1.5), roken (odds ratio 2.2) of de aanwezigheid van coronairlijden (odds ratio 1.8). Deze bevindingen zijn vooral van belang in die gevallen die niet voldoen aan het klassieke klinische patroon.

Onze multivariabele diagnostische modellen ondersteunen de intuïtieve schatting

van de kans op perifeer arterieel vaatlijden die een huisarts heeft na iedere fase van zijn klinische evaluatie van de patiënt. Bij veel patiënten zal hij ziekte kunnen uitsluiten met een hoge mate van zekerheid (60% van alle benen in onze onderzoekspopulatie had een voorspelde kans op perifeer arterieel vaatlijden $< 5\%$). Bij een kleine groep patiënten kan hij een met een hoge mate van zekerheid de diagnose perifeer arterieel vaatlijden stellen (1.3% van alle benen in ons onderzoek had een voorspelde kans op perifeer arterieel vaatlijden $> 80\%$). Als de kans op perifeer arterieel vaatlijden niet laag genoeg is om de aandoening te mogen uitsluiten, maar niet hoog genoeg om de diagnose te kunnen stellen (in onze onderzoekspopulatie had 38% van alle benen een voorspelde kans op perifeer arterieel vaatlijden tussen 5 en 80%), zou de huisarts het (laten) doen van niet-invasief vaatonderzoek kunnen overwegen om zijn diagnostische onzekerheid te verkleinen.

Samenvattend: onze analyse laat zien dat traditionele klinische diagnostiek de huisarts voldoende gegevens oplevert om een zinnige beslissing te kunnen nemen over de noodzaak van aanvullende diagnostiek of therapie bij patiënten met klachten verdacht voor perifeer arterieel vaatlijden. Het zou nuttig zijn als onze diagnostische modellen extern gevalideerd zouden worden door ze uit te testen in een vergelijkbare onderzoekspopulatie.

In *hoofdstuk 11* worden de belangrijkste resultaten van ons onderzoek besproken in relatie tot onze vraagstellingen en recente literatuur. Ook wijden we een beschouwing aan diverse methodologische aspecten, worden de consequenties van onze resultaten voor de huisartspraktijk besproken en worden enkele ideeën voor verder onderzoek gepresenteerd.

Ons onderzoek maakt duidelijk dat de huisarts in vele gevallen de hypothese dat perifeer arterieel vaatlijden aanwezig is kan verwerpen of bevestigen op basis van anamnese, lichamelijk onderzoek en groene kaartgegevens. Als dat niet met voldoende zekerheid mogelijk is, kan de huisarts het pocket-Doppler apparaat gebruiken om de EA-index te bepalen en zo zijn diagnostische onzekerheid te verminderen. De bepaling van de EA-index in de huisartspraktijk bleek reproduceerbaar en valide. We konden praktische beslisregels voor de bepaling en de interpretatie van de EA-index opstellen.

De resultaten van ons onderzoek kunnen een bijdrage leveren aan goede werkafspraken tussen huisartsen, vasculaire functie-afdelingen en vaatspecialisten omtrent het gebruik van niet-invasief vaatonderzoek door de huisarts.

De notie dat perifeer arterieel vaatlijden een uiting is van gegeneraliseerde atherosclerose dient praktische consequenties te hebben voor de huisarts. Ons onderzoek laat zien dat de huisarts zijn feitelijk handelen met betrekking tot de secundaire preventie van hart- en vaatziekten nog kan aanscherpen.

In de nabije toekomst hopen we resultaten te kunnen publiceren over de conservatieve behandeling van perifeer arterieel vaatlijden, over indicatoren met betrekking tot de prognose van de aandoening en over de klinische relevantie van asymptomatisch perifeer arterieel vaatlijden. Ons huidige databestand kan gebruikt worden om een alternatieve analyse van diagnostische gegevens te testen.

Er is meer onderzoek nodig op het gebied van de 'quality of life' van patiënten met perifeer arterieel vaatlijden. Ook zou het nuttig zijn onderzoek te doen naar het effect van het gebruik van het pocket-Doppler-apparaat door huisartsen op de hoeveelheid, de kwaliteit en het uiteindelijke resultaat van verwijzingen naar de

vaatspecialist.

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Bij de uitvoering van aandoeningsgericht patientgebonden onderzoek nemen de huisartsen en praktijkassistenten die de gegevens verzamelen een centrale plaats in. Aan dit onderzoek werd loyaal meegewerkt door: *Piet Athmer* (Kerkrade); *George Beusmans*, *Nandus Vierhout*, *Annemiek Franssen*, *Edith Dubislav* (Maastricht); *Ankie Westers*, *Marjo van Bommel*, *Tiny van Merode*, *Thelma l'Espoir* (Maastricht); *Frank Guldemon*, *Jeannie Spiertz* (Ubachsberg); *Paul Hulshof*, *Rudolf Panhuysen*, *Yvonne Guldemon-Hecker*, *Ingeborg Soomers*, *Yvonne Sintzen*, *Petra Senden*, *Geja Dialektopoulos-van Putten*, *Sep Schmeets* (Voerendaal); *Bert ten Berge*, *Pieter van der Heyden*, *May van Bilsen* (Roermond); *Willem Nieuwdorp*, *Yvonne Draaisma*, *Marjo Neelis*, *Anja Savelkoul*, *Marina Gösgens*, *Marion Theunissen* (Brunssum); *They Lemmens*[†], *Paul Stalenhoef*, *Bér Huynen*, *Pie Castermans*, *Lilian Claessens*, *Riet Hautvast*, *Lilian Wijnands*, *Linda van Laar* (Maastricht); *Henk Logister*[†], *Bert van de Werf*, *Mary Busscher*, *Anuschka Westhoff*, *René Janssen* (Heerlen); *Geertje van Zanten*, *Jan Michels*, *Dirk van der Wissel*, *Giaconda Rutzerveld-Verspagen*, *Marina Oosterhuis*, *Hannie Drieman*, *Marjo Konings* (Kerkrade); *Bart Otten*, *Renate Trienes* (Merkelbeek); *Giel Peeters*, *Frans Vissers*, *Marion Frijns*, *Chris Grundlach*, *Marie-Louise de Bruyn* (Maastricht); *Erwin Vijgen*, *Resi Vijgen-Hamers*, *Lilian Otten* (Geleen); *Ton van Dam*, *Chris Hanssen* (Kerkrade); *Harrie Eussen*, *Hans Ypma*, *Carla Stuurman* (Landgraaf); *Eef Hubbers* (Kerkrade); *Frank Soomers*, *Suzanne van Schijndel* (Kerkrade); *Pierre Passage*, *Jan Drenth*, *Gerda Salden* (Kerkrade). Via hen wil ik ook alle patiënten die meededen bedanken.

Extra werkzaamheden werden verricht door de praktijkassistenten *Edith Dubislav*, *Riet Hautvast*, *Linda van Laar*, *Marion Frijns*, *Chris Grundlach* en *Marie-Louise de Bruyn* in verband met het 'Doppler-valideringsonderzoek'. *Ingeborg Soomers* en *Marie-Louise de Bruyn* verzorgden Doppler-demonstraties tijdens het N.H.G.-congres van 1989 in Den Haag.

Ondanks de verhuizing van het Academisch Ziekenhuis Maastricht van Annadal naar Randwijck werd de uitvoering van het 'Doppler-valideringsonderzoek' een succes dankzij de enthousiaste medewerkers van 'het vaatlab': *Yvonne Reijnders*, secretaresse, *Edith Ermers* en *Monique Kuypers*, vaatlaborantes.

Jan Klerkx, tolk-vertaler, corrigeerde het Engels van hoofdstuk 7 en *David Warn-dorff*, arts en native speaker, vertaalde in sneltreinvaart de hoofdstukken 1 tot en met 6 in het Engels. *Irene Korstjens* gaf adviezen over de Nederlandstalige onderdelen van dit proefschrift.

Jan Rauwerda, hoogleraar vaatchirurgie, *Chris van Weel*, hoogleraar huisartsgeneeskunde, *Paul Knipschild*, hoogleraar epidemiologie, *Ton Gorgels*, universitair hoofddocent cardiologie en *Peter Pop*, hoogleraar transmurale geneeskunde beoordeelden het concept-proefschrift.

Voor de vormgeving van het binnenwerk van het proefschrift ontving ik gevraagde en ongevraagde tips van *Jan Leewis*, *Michiel Cornel*, *Manuel Stoffers*, *Piet Portegijs*,

Ruud Leliveld en Wendy Verhagen. Het omslag werd ontworpen door *Wendy Verhagen* (Datawyse).

Agnes Deckers (Hoechst) bood me de mogelijkheid het proefschrift een ruimere bekendheid te geven door verspreiding onder een groep geïnteresseerde huisartsen financieel te ondersteunen.

Aan *Victor Kaiser, Michiel Cornel, Saskia Mol en George Wolfs*, mijn Maastrichtse collega's, had ik prima kamergenoten. Ik heb veel gehad aan de discussies met Michiel over de toepassing van multiple logistische regressie bij diagnostisch onderzoek.

Frank Soomers en Marianne Soomers-Turlings, mijn Kerkraadse collega's, hebben ervoor gezorgd dat ik meer huisarts ben geworden en dat ik nog steeds huisarts ben en denk te blijven. 'Academisering' is in deze praktijk een werkbaar ontwikkelingsproces gebleken.

Peter Kitslaar, hoogleraar algemene heelkunde, was de opvolger van Paul Jörning in de projectgroep en mijn tweede promotor. Als toenmalig hoofd van het Vaatlaboratorium maakte hij het 'Doppler-valideringsonderzoek' mogelijk. In de laatste jaren van het project leverde hij met grote deskundigheid kritische en constructieve bijdragen aan de analyse en rapportage van het project.

Op *Arnold Kester*, als statisticus bij het project betrokken, deed ik de afgelopen jaren nooit tevergeefs een beroep. Hij bedacht degelijke oplossingen voor niet-alledaagse analyse-problemen.

Paula Rinkens was de research-assistente van dit deel van het PAV-Project. Zij was voortdurend een betrokken en creatieve gesprekspartner die met name in de analysefase van het onderzoek een ware rots in de branding bleek te zijn.

Victor Kaiser, huisarts-onderzoeker, was de 'eerste' onderzoeker van het PAV-Project en mijn vaste kamergenoot in al die jaren. De voorbereiding van het project inclusief het werven van huisartsen voor dit onderzoek, is voor een belangrijk deel zijn werk geweest. Na de gemeenschappelijke fase van de gegevensverzameling bleef hij als meedenker en co-auteur zijn bijdragen leveren aan mijn deel van het project. Zijn eigen dissertatie volgt binnenkort.

André Knottnerus, hoogleraar Huisartsgeneeskunde, was de projectleider van het onderzoek en mijn promotor. Hij gaf mij de ruimte en stuurde soepel bij. Ondanks het feit dat in de onderzoeksperiode extra velen een appél op hem deden, bleef hij een stimulerende en enthousiaste begeleider.

Curriculum Vitae

Henri ('Jelle') Stoffers was born on July 5th 1957 in Heerlen, the Netherlands. Eldest of five children of a teachers' couple he grew up in Hoensbroek and Schaesberg, villages in the former Limburg mining district. He finished his secondary education, Athenaeum-B, at the 'Eijkhagencollege' in Schaesberg in 1975. He studied medicine at the Catholic University of Nijmegen from 1975 to 1983. As an alternative to military service he worked as a physician in the 'Humanitaskliniek', a nursing and revalidation hospital in Rotterdam (1984-1985).

During his vocational training (Nijmegen University Institute of Family Practice) he worked as GP trainee in the practice of Elbert van Ruller in Arnhem (1985-1986). During the year 1986-1987 he combined working as a general practitioner with the experimental GP research training of the University of Limburg in Maastricht. He received a grant from the Netherlands Organization for Scientific Research to work on the present study (1988-1991). In 1992 he became a staff member of the Department of General Practice, spending his time on research and undergraduate teaching. From 1989 he also works as a general practitioner in a group practice (with Frank Soomers and Marianne Soomers-Turlings) in Kerkrade. Jelle Stoffers lives in Maastricht, is married and has three children.

Appendices

Appendix chapter 3 The measurement of the ankle-brachial systolic pressure ratio (AB-ratio) by means of a pocket Doppler device

Required are a pocket Doppler device with a transducer suitable for arteries (8 Mhz, possibly 5 MHz), a calibrated mercury sphygmomanometer with a cuff of at least 12 cm and aqueous gel. The price of a pocket Doppler device varies from f 700,- to f 2000,- depending on the type.

The measurement (of both legs and both arms) may be carried out by the general practitioner as well as by a practice assistant in approximately 10-20 minutes, depending on the experience of the investigator and the level of difficulty of the patient. The examination room should be properly heated. Prior to the actual measurement, the patient is asked to lie down as flat as possible on the examination couch. The sequence of the measurements is: arm-leg-other leg-other arm. Particular attention should be paid to proper fixation of the transducer and to slow release of the cuff pressure. After the measurements are made, the Doppler device is to be shut off and stored carefully: the transducer is extremely vulnerable!

The procedure for a leg is as follows:

- 1 Apply the sphygmomanometer just proximal to the malleoli of the leg, with the tubes in an upward position.
- 2 Palpate the posterior tibial artery dorsal to the medial malleolus.
- 3 Apply some aqueous gel at this location, even when the artery is palpable.
- 4 Switch on the Doppler device and position the transducer in the gel at an angle of 30 to 60 degrees to the artery. Search for the best arterial signal.
- 5 In case no signal is obtained in this location, take the dorsalis pedis artery.
- 6 Keep the transducer well fixed and use your other hand to inflate the cuff up to approximately 30 mmHg higher than the reading at which the signal disappears.
- 7 Deflate the cuff very slowly; best is a rate of 2mmHg per second. Note the reading at which the arterial signal is first audible. Never reinflate the cuff during the measurement, but deflate the cuff completely if the transducer moves.

The procedure is repeated for the other leg (items 1-7).

The radial artery at the level of the wrist is used for the measurement of the systolic brachial pressure; the procedure is analogous to that for the legs (item 3, 4, 6, 7).

The AB-ratio is computed for each leg by dividing the systolic ankle pressure by the highest systolic brachial pressure.

Appendix Chapter 5

Appendix 5.1 Participating General Practice Centres

- 1 Huisartspraktijk P. Athmer, Kerkrade
- 2 Gezondheidscentrum 'De Hofhoek' (G.H.M.I. Beusmans, W.P.M. Vierhout), Maastricht
- 3 Huisartspraktijk T. van Merode, M. van Bommel, Maastricht
- 5 Huisartspraktijk F.I. Guldemon, Ubachsberg
- 6 Huisartspraktijk P.B.N. Hulshof, R.A.M. Panhuysen, E.T.I.M. Guldemon-Hecker, Voerendaal
- 7 Gezondheidscentrum 'Maasniel' (A.A. ten Berge, P.F.M. van der Heyden), Roermond
- 8 Huisartspraktijk W.M.H. Nieuwdorp, Brunssum
- 9 Gezondheidscentrum 'Dr. van Kleef' (Th.G.J. Lemmens[†], P.A. Stalenhoef, L.G.J. Huynen, G.A.H.M. Castermans), Maastricht
- 10 Huisartspraktijk H. Logister[†], B.T.M.G. van der Werf, Heerlen
- 11 Gezondheidscentrum 'De Maar' (G. van Zanten, J.J. Michels, H.A.W.J. van der Wissel), Kerkrade
- 12 Huisartspraktijk B.H.J.M. Otten, Merkelbeek
- 14 Gezondheidscentrum 'Heer' (M.P.J.M. Peeters, F.H.J.A. Vissers), Maastricht
- 15 Huisartspraktijk E.S.M. Vijgen, T.A.H. Vijgen-Hamers, Geleen
- 16 Huisartspraktijk A. van Dam, Ch. Hanssen, Kerkrade
- 17 Huisartspraktijk J.H.M. Eussen, J.A.M. Ypma, C. Stuurman, Landgraaf
- 18 Huisartspraktijk E.H.J.F. Hubbers, Kerkrade
- 19 Huisartspraktijk F.L.M. Soomers, J.M.S.J.G. Soomers-Turlings, Kerkrade
- 20 Huisartspraktijk P.H.M. Passage, J.H.J. Drenth, Kerkrade

Appendix 5.2 The Postal Questionnaire

- 'VRAGENLIJST', 1 page

Appendix 5.3 Registration Forms

- 'VRAGENLIJST PAV-PROJECT LIMBURG', 11 pages
- 'PRAKTIJK-ONDERZOEKSLIJST PAV-PROJECT LIMBURG', 8 pages

VRAGENLIJST

1. Kloppen de bovenstaande persoonsgegevens ?	0 ja	0 nee
Indien nee, hoe luiden deze dan ?		
Naam		
Adres		
Postcode/woonplaats		
2. Wat is uw geboortedatum ?		
dag, maand, jaar/...../.....		
Wat is uw geslacht ?		
man / vrouw (doorhalen wat niet van toepassing is)		
3. Krijgt u pijn (kramp, loom gevoel enz.) in de kuit en/of benen bij het lopen ?	0 ja	0 nee
4. Heeft u vaak last van koude voeten ?	0 ja	0 nee
5. Rookt u meer dan 15 sigaretten gemiddeld per dag ?	0 ja	0 nee
6. Wordt u behandeld voor hoge bloeddruk ?	0 ja	0 nee
7. Heeft u suikerziekte ?	0 ja	0 nee
8. Bent u ooit onder behandeling geweest voor een hartkwaal of beroerte ?	0 ja	0 nee
9. Komen er in de familie mensen voor (broer, zus, vader, moeder, oom, tante, opa, oma) die een hartkwaal of een beroerte gehad hebben ?	0 ja	0 nee

Controleer of u geen vragen vergeten bent.

U wordt verzocht de vragenlijst m.b.v. de bijgevoegde retourenveloppe (postzegel niet nodig) binnen drie weken terug te sturen.

Bedankt voor uw medewerking.

VRAGENLIJST

PAV-PROJECT LIMBURG

Diagnostiek van bloedvatvernauwing
in de benen
door de huisarts

Personalia

Zijn bovenstaande gegevens correct en volledig?

Zo nee, vul dan hier beneden de juiste of ontbrekende gegevens in.

naam: voorletters:

adres:

postcode:

woonplaats:

Houdt de toelichting bij de hand.

Datum (dag waarop u de lijst invult): _____ - _____ -19

Geboortedatum: - -19

☐ Man ☐ Vrouw

Wat is of was uw beroep?: _____

Vragen:

- 1 Als u op straat loopt, krijgt u dan op een gegeven moment, tijdens het lopen, last van een of beide benen?**

- ☐₁ ja
- ☐₂ nee
- ☐₃ ik loop nooit op straat

- 2 En als u haastig loopt of een heuvel op: krijgt u dan last?**

- ☐1 ja
- ☐2 nee
- ☐3 ik loop nooit haastig of een heuvel op

Doe nu het volgende:

- als u één of beide vragen met "ja" beantwoord heeft, ga dan verder met vraag 3 t/m 14
- anders gaat u verder met vraag 15

Deze kolom
niet invullen

 1-7
 8

 9-14

 15-20

 21

22

Tijdens het lopen krijgt u dus, in meer of mindere mate, last van een of beide benen.

Ga verder met de volgende vragen. Lees eerst de "Toelichting".

Vul bij de vragen 3 t/m 6 beide benen in. U mag bij deze vragen méér dan één hokje per regel aankruisen.

3 Krijgt u last van kramp, en zo ja waar?

	geen kramp	tenen	voet	kuit	boven- been	heup	bil
	1	2	3	4	5	6	7
Linkerbeen:	☐	☐	☐	☐	☐	☐	☐
Rechterbeen:	☐	☐	☐	☐	☐	☐	☐

24-29							
30-35							

4 Krijgt u last van pijn, en zo ja, waar?

	geen pijn	tenen	voet	kuit	boven- been	heup	bil
	1	2	3	4	5	6	7
Linkerbeen:	☐	☐	☐	☐	☐	☐	☐
Rechterbeen:	☐	☐	☐	☐	☐	☐	☐

36-41							
42-47							

5 Krijgt u last van een moe of zwak gevoel, en zo ja waar?

	geen last van moe of zwak gevoel	tenen	voet	kuit	boven- been	heup	bil
	1	2	3	4	5	6	7
Linkerbeen:	☐	☐	☐	☐	☐	☐	☐
Rechterbeen:	☐	☐	☐	☐	☐	☐	☐

48-53							
54-59							

6 Krijgt u last van een doof of tintelend gevoel, en zo ja, waar?

	geen last van een dof of tintelend gevoel	tenen	voet	kuit	boven- been	heup	bil
	1	2	3	4	5	6	7
Linkerbeen:	☐	☐	☐	☐	☐	☐	☐
Rechterbeen:	☐	☐	☐	☐	☐	☐	☐

60-65							
66-71							

7 Krijgt u last van andere klachten in de benen tijdens het lopen, die we hierboven niet genoemd hebben?

☐1 ja,
schrijf dan hieronder in uw eigen woorden wát u voelt:

☐2 nee

72							
73-74							

Bij de vragen 8 t/m 11 mag u maar 1 hokje per vraag aankruisen

8 Als u last krijgt, wat doet u dan meestal?

- ☐₁ ik loop door in hetzelfde tempo
☐₂ ik ga langzamer lopen
☐₃ ik stop

☐

75

9 Stel u krijgt last van een of beide benen tijdens het lopen, en u loopt door. Wat gebeurt er dan met uw klacht of klachten?

- ☐₁ meestal wordt het erger
☐₂ soms wordt het erger, soms blijft het hetzelfde
☐₃ meestal blijft het hetzelfde
☐₄ soms blijft het hetzelfde, soms wordt het minder erg
☐₅ meestal wordt het minder erg of verdwijnt

☐

76

10 En wat gebeurt er als u niet doorloopt, maar stil gaat staan?

- ☐₁ meestal wordt het erger
☐₂ soms wordt het erger, soms blijft het hetzelfde
☐₃ meestal blijft het hetzelfde
☐₄ soms blijft het hetzelfde, soms wordt het minder erg
☐₅ meestal wordt het minder erg of verdwijnt

☐

77

11 En wat gebeurt er als u niet doorloopt, maar gaat zitten?

- ☐₁ meestal wordt het erger
☐₂ soms wordt het erger, soms blijft het hetzelfde
☐₃ meestal blijft het hetzelfde
☐₄ soms blijft het hetzelfde, soms wordt het minder erg
☐₅ meestal wordt het minder erg of verdwijnt
☐₆ ik ga dan nooit zitten

☐

78

Ga verder met vraag 12

Bij de vragen 12 t/m 14 mag u maar 1 hokje per vraag aankruisen

Deze kolom
niet invullen

Tijdens het lopen krijgt u in meer of mindere mate klachten in een of beide benen.

- 12 Hoeveel hinder ondervindt u daarvan bij de uitvoering van uw werkzaamheden (betaalde baan, huishoudelijk werk, vrijwilligerswerk, studie en dergelijke)?**

- ☐ 1 zeer veel
☐ 2 veel
☐ 3 weinig
☐ 4 geen

☐

79

- 13 Hoeveel hinder ondervindt u daarvan bij activiteiten die u graag onderneemt in uw vrije tijd (sport, hobbies, uitstapjes, uitgaan, film- en theaterbezoek en dergelijke)?**

- ☐ 1 zeer veel
☐ 2 veel
☐ 3 weinig
☐ 4 geen

☐

80

- 14 Hoeveel hinder ondervindt u daarvan bij het onderhouden van uw sociale contacten (bezoek aan familie, vrienden, kennissen en dergelijke)?**

- ☐ 1 zeer veel
☐ 2 veel
☐ 3 weinig
☐ 4 geen

☐	☐	☐	☐	☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------

1-7

☐ 2

8

☐

9

Ga verder met vraag 15

Bij de vragen 15 t/m 17 moet u beide benen invullen. Lees eerst de "Toelichting". U mag maar 1 hokje per regel aankruisen.

15 Als u ('s nachts) in bed ligt, heeft u dan last van pijnlijke krampen in uw kuit?

	altijd	vaak	soms	nooit
	1	2	3	4
Linkerbeen:	☐	☐	☐	☐
Rechterbeen:	☐	☐	☐	☐

☐

10

☐

11

16 Als u ('s nachts) in bed ligt, heeft u dan last van tintelingen in uw voet of tenen?

	altijd	vaak	soms	nooit
	1	2	3	4
Linkerbeen:	☐	☐	☐	☐
Rechterbeen:	☐	☐	☐	☐

☐

12

☐

13

17 Als u ('s nachts) in bed ligt, heeft u dan last van pijn in uw voet of tenen?

	altijd	vaak	soms	nooit
	1	2	3	4
Linkerbeen:	☐	☐	☐	☐
Rechterbeen:	☐	☐	☐	☐

☐

14

☐

15

18 Als u ('s nachts) in bed ligt, heeft u dan last van andere klachten in een of beide benen (daarmee wordt alles van bil tot tenen bedoeld), die we hierboven niet genoemd hebben?

- ☐₁ ja,
schrijf dan hieronder wát u voelt:

- ☐₂ nee

☐

16

☐

17-18

19 Als u ('s nachts) in bed last hééft van een of beide benen, wat gebeurt er dan als u uw benen buiten bed laat bungelen?

- ☐₁ het wordt erger
☐₂ het blijft hetzelfde
☐₃ het wordt minder erg
☐₄ ik heb dit nooit uitprobeerde
☐₅ ik heb nooit last van mijn benen als ik ('s nachts) in bed lig

☐

19

Ga verder met vraag 20

20 Heeft u last van koude voeten?

- ☐₁ ja
☐₂ nee

Zo nee, mannen: ga door naar vraag 24
 vrouwen: ga door naar vraag 25

Deze kolom
niet invullen

☐

20

De vragen 21 t/m 23 alleen invullen als u vraag 20 met "ja" beantwoord heeft

21 U heeft last van koude voeten. Aan welke voet?

- ☐₁ beide voeten
☐₂ alleen linkervoet
☐₃ alleen rechtervoet

☐

21

22 Wanneer heeft u last van koude voeten? (1 hokje aankruisen)

- ☐₁ als ik loop
☐₂ als ik zit of sta
☐₃ als ik lig
☐₄ dat kan ik niet precies aangeven

☐

22

23 Vul in: hoe lang heeft u al last van koude voeten?

..... jaar en maanden

☐ ☐ ☐ ☐

23-26

Vraag 24 is alleen bedoeld voor mannen; vrouwen: ga door naar vraag 25

- 24** De volgende vraag zal u misschien verbazen. We stellen hem, omdat we duidelijk willen weten, welke klachten mensen met bloedvatvernauwing in de benen hebben. Het komt soms voor, dat een man met bloedvatvernauwing geen stijf geslachtsorgaan kan krijgen, terwijl dat vroeger wel gebeurde. Overigens heeft deze klacht meestal een andere oorzaak dan bloedvatvernauwing!
Onze vraag is: heeft u problemen gekregen met het stijf worden van uw geslachtsorgaan (terwijl u daar vroeger of eerder geen problemen mee had)?

- ☐₁ ja
☐₂ nee

☐

27

Ga nu door met vraag 25

Bij de vragen 25 t/m 29 moet u beide benen invullen. U mag maar een hokje per regel aankruisen. Lees eerst de "Toelichting".

Deze kolom
niet invullen

25 Als u een tijd lang zit, krijgt u dán last van een of beide benen?

	altijd	vaak	soms	nooit
	1	2	3	4
Linkerbeen:	☐	☐	☐	☐
Rechterbeen:	☐	☐	☐	☐

☐
☐

28

☐
☐

29

26 Als u een tijd lang staat, krijgt u dán last van een of beide benen?

	altijd	vaak	soms	nooit
	1	2	3	4
Linkerbeen:	☐	☐	☐	☐
Rechterbeen:	☐	☐	☐	☐

☐
☐

30

☐
☐

31

27 Krijgt u klachten in een of beide benen als u achteroverbuigt met uw rug?

	altijd	vaak	soms	nooit	ik buig nooit achter- over
	1	2	3	4	5
Linkerbeen:	☐	☐	☐	☐	☐
Rechterbeen:	☐	☐	☐	☐	☐

☐
☐

32

☐
☐

33

28 Krijgt u klachten in een of beide benen als u fietst?

	altijd	vaak	soms	nooit	ik fiets nooit
	1	2	3	4	5
Linkerbeen:	☐	☐	☐	☐	☐
Rechterbeen:	☐	☐	☐	☐	☐

☐
☐

34

☐
☐

35

29 Krijgt u last van een of beide benen als u aan het joggen of trimmen bent?

	altijd	vaak	soms	nooit	ik trim of jog nooit
	1	2	3	4	5
Linkerbeen:	☐	☐	☐	☐	☐
Rechterbeen:	☐	☐	☐	☐	☐

☐
☐

36

☐
☐

37

Ga door met vraag 30

30 Rookt u? (1 hokje aankruisen)

- ☐₁ ja, ik rook
Ga door met vraag 31
- ☐₂ nee, maar ik heb wel gerookt
Ga door met vraag 32
- ☐₃ nee, en ik heb ook nooit gerookt
Ga door met vraag 33

☐

38

31 Alleen invullen als u bij vraag 30 hokje "1" heeft aangekruist

Vul in (op alle regels een getal invullen):

Ik rook:

..... jaar,
..... sigaretten (gemiddeld) per dag
..... sigaren (gemiddeld) per dag
..... pijpen (gemiddeld) per dag

Ga nu door met vraag 33

39-40

41-42

43-44

45-46

32 Alleen invullen als u bij vraag 30 hokje "2" heeft aangekruist

Vul in (op alle regels een getal invullen):

Ik ben jaar geleden gestopt

Ik heb jaar gerookt

Ik rookte toen sigaretten (gemiddeld) per dag

..... sigaren (gemiddeld) per dag

..... pijpen (gemiddeld) per dag

Ga nu door met vraag 33

47-48

49-50

51-52

53-54

55-56

33 Hebben een of meer van uw eigen familieleden (dus: oma's, opa's, vader, moeder, broer of zus van vader, broer of zus van moeder, uw eigen broer of zus, uw eigen zoon of dochter), een of meer van de volgende ziekten gehad:

- hartklachten, hartinfarct, hartverlamming; hersenbloeding, beroerte, attaque, halfzijdige verlamming, bloedvatvernauwing in de hals, bloedvatvernauwing in de benen?

- ☐₁ ja
☐₂ nee

☐

57

Ga door met vraag 34

Deze kolom
niet invullen

34 Als u medicijnen in huis heeft tegen pijn (hoofdpijn, spierpijn, rugpijn, menstruatiepijn en dergelijke), griep of koorts, die u zonder recept bij de drogist of apotheek heeft gekocht, kunt u dan hieronder opschrijven:

- de naam van dat medicijn of die medicijnen (invullen), en
- hoe vaak u ieder medicijn gemiddeld gebruikt: dagelijks, wekelijks of nog minder vaak (aankruisen)

(Zie de "Toelichting" bij vraag 34)

	ik gebruik dit dagelijks	ik gebruik dit wekelijks	ik gebruik dit minder vaak
Naam medicijn	1	2	3
a	☐	☐	☐
b	☐	☐	☐
c	☐	☐	☐
d	☐	☐	☐

e Ik gebruik nooit medicijnen waarvoor ik geen recept nodig heb. ☐

Ga door met de vragen 35, 36 en 37.

☐

58-59

In welke groep deelt u uw werkzaamheden (betaalde baan, huishoudelijk werk, vrijwilligerswerk, studie en dergelijke) in, voor wat betreft lichaamsbeweging?

35 – Houding: (1 hokje aankruisen)

- ☐1 hoofdzakelijk lopend
- ☐2 zittend en staand, soms lopend
- ☐3 hoofdzakelijk zittend

☐

60

36 – Lichamelijke inspanning: (1 hokje aankruisen)

- ☐1 zware lichamelijke inspanning
- ☐2 matig zware lichamelijke inspanning
- ☐3 lichte lichamelijke inspanning

☐

61

37 In welke groep deelt u uw bezigheden in uw vrije tijd (sport, hobbies, uitstapjes, uitgaan, film- en theaterbezoek en dergelijke) in, wat betreft lichaamsbeweging?

- ☐1 veel lichaamsbeweging
- ☐2 niet veel, maar ook niet weinig lichaamsbeweging
- ☐3 weinig lichaamsbeweging

☐

62

Ga door naar de volgende bladzijde.

Vraag 37 was de laatste vraag.

Loopt u alle vragen nog eens na?

Heeft u alles ingevuld wat u in moest vullen?

Zijn uw naam, voorletters, adres, geboortedatum, geslacht en beroep correct ingevuld?

Heeft u de datum van vandaag (boven op pagina 1) ingevuld?

Neem uw vragenlijst mee naar uw huisarts.

Uw huisarts zal deze doorlezen.

Daarna gaat uw huisarts verder met het onderzoek.

HARTELIJK DANK !

PRAKTIJK-ONDERZOEKSLIJST

PAV-PROJECT LIMBURG

Diagnostiek van bloedvatvernauwing
in de benen
door de huisarts

Lichamelijk onderzoek
groene kaart
klinische diagnose
e-a-index I
e-a-index II
evaluatie

Personalia

Lees eerst de instructie en houdt deze bij de hand tijdens het invullen van deze formulieren.

Lichamelijk onderzoek

Lees eerst de instructie

Datum - -19

Onderzoekend huisarts

Onderzoeksnummer

Deze kolom
niet invullen

3									1-7
									8
									9-14

									15-17
									18-20
									21-23
									24-26
									27-29
									30
									31
									32

ALGEMEEN

- 1 Lengte (cm):
- 2 Gewicht (kg):
- 3 Pols (puls./min.)
- 4 Syst. tensie (mm Hg):
- 5 Diast. tensie (mm Hg):
- 6 Cor: ictus

☐1 < mcl
☐2 > mcl
☐3 niet palpabel
- 7 Cor: regulair?

☐1 ja
☐2 nee
- 8 Cor: souffle?

☐1 ja
☐2 nee

BEHARINGSPATROON BENEN

- 9 Links-rechts-verschil?

☐1 ja, links minder
☐2 ja, rechts minder
☐3 nee, geen li-re-verschil

									33
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ULCERA AAN TENEN OF VOORVOET?

ja nee

1 2

- 10 a Links ☐ ☐
- b Rechts ☐ ☐

									34
									35

ULCUS AAN HET ONDERBEEN?

ja, mediaal ja, lateraal nee

1 2 3

- 11 a Links ☐ ☐ ☐
- b Rechts ☐ ☐ ☐

									36
									37

KLEUR VOET EN ONDERBEEN (liggend)

12 bleek rood blauw normaal

1 2 3 4

- a Links ☐ ☐ ☐ ☐
- b Rechts ☐ ☐ ☐ ☐

									38
									39

TEMPERATUUR VOETRUG

- 13 Links-rechts-temperatuurverschil?
- ☐₁ ja, links kouder
- ☐₂ ja, rechts kouder
- ☐₃ nee, geen li-re-verschil

Deze kolom
niet invullen

☐ 40

PALPATIE PERIFERE PULSATIES

- | | sterk
1 | zwak
2 | afwezig
3 | | |
|------------------|--------------------------|--------------------------|--------------------------|--------------------------|----|
| 14 A. Femoralis | | | | ☐ | 41 |
| a Links | ☐ | ☐ | ☐ | ☐ | |
| b Rechts | ☐ | ☐ | ☐ | ☐ | 42 |
| 15 A. Tib. Post. | | | | ☐ | 43 |
| a Links | ☐ | ☐ | ☐ | ☐ | |
| b Rechts | ☐ | ☐ | ☐ | ☐ | 44 |
| 16 A. Dors. Ped. | | | | ☐ | 45 |
| a Links | ☐ | ☐ | ☐ | ☐ | |
| b Rechts | ☐ | ☐ | ☐ | ☐ | 46 |

AUSCULTATIE

souffle:

- | | aanwezig
1 | afwezig
2 | | |
|----------------------|--------------------------|--------------------------|--------------------------|----|
| 17 Aorta Abdominalis | ☐ | ☐ | ☐ | 47 |
| 18 A. Femoralis | | | ☐ | 48 |
| a Links | ☐ | ☐ | ☐ | |
| b Rechts | ☐ | ☐ | ☐ | 49 |

Vul nu de **groene-kaart-gegevens** in op de volgende pagina.

Gegevens groene kaart

Lees eerst de instructie.

RISICOFACTOREN

Geef aan, of de patiënt bij u bekend is met de volgende risicofactoren voor PAV:

19	angina pectoris	☐ 1 ja	☐ 2 nee
20	myocard-infarct	☐ 1 ja	☐ 2 nee
21	T.I.A.	☐ 1 ja	☐ 2 nee
22	C.V.A.	☐ 1 ja	☐ 2 nee
23	hypertensie	☐ 1 ja	☐ 2 nee
24	hypercholesterolemie	☐ 1 ja	☐ 2 nee
25	overgewicht	☐ 1 ja	☐ 2 nee
26	diabetes mellitus	☐ 1 ja	☐ 2 nee

Zo ja, door naar 27 en 28

Zo nee, door naar 29

27	D.M.: welk type?	☐ 1 I	☐ 2 II
28	D.M.: goed gereguleerd?	☐ 1 ja	☐ 2 nee

OPERATIE- EN AMPUTATIESTATUS

29	Operatie i.v.m. PAV (m.u.v. amputatie)?	☐ 1 ja	☐ 2 nee

Zo ja, door met vraag 30

Zo nee, door met vraag 31

30	Welke operatie (z. n. links-rechts vermelden)?	
31	Amputatie i.v.m. PAV?	☐ 1 ja ☐ 2 nee

Zo ja, door met vraag 32

Zo nee, door met vraag 33

32	Geef het amputatie-nivo aan:	

	teen	voor- voet	enkel	onder- been	boven- been	geen amputatie
	1	2	3	4	5	6
a Links	☐	☐	☐	☐	☐	☐
b Rechts	☐	☐	☐	☐	☐	☐

VOORGESCHREVEN ONDERHOUDSMEDICATIE

33	Naam	Dosering

a		
b		
c		
d		
e		
f		
g		

3

Deze kolom
niet invullen

☐	50
☐	51
☐	52
☐	53
☐	54
☐	55
☐	56
☐	57
☐	58
☐	59
☐	60
☐	61-62
☐	63
☐	64
☐	65
☐	66-67
☐	68-69
☐	70-71
☐	72-73
☐	74-75
☐	76-77
☐	78-79

Klinische diagnose

Lees eerst de instructie.

34 Uw diagnose op dit moment is:

- ☐ 1 deze patiënt heeft hoogstwaarschijnlijk **PAV**
(door met **vraag 35**)
- ☐ 2 deze patiënt heeft **mogelijk PAV**
(door met **vraag 35**)
- ☐ 3 deze patiënt heeft waarschijnlijk **geen PAV**
(door met **vraag 36**)

35 Deze patiënt heeft hoogstwaarschijnlijk of mogelijk PAV;
a aan **welk been?**

- ☐ 1 links
- ☐ 2 rechts
- ☐ 3 beide

b mate van **ernst?**

- ☐ 1 geen klachten
- ☐ 2 claudicatie, weinig invaliderend
- ☐ 3 claudicatie, erg invaliderend
- ☐ 4 rustpijn / nachtpijn / trofische stoornissen
- ☐ 5 gangreen

c was patiënt (bij u) **bekend** met, of **verdacht** voor PAV, vóór dit onderzoek?

- ☐ 1 ja
- ☐ 2 nee

d lijdt deze patiënt **daarnaast óók** aan **andere aandoeningen** van zijn/haar been?

- ☐ 1 ja (door met **vraag e**)
- ☐ 2 nee

e om **welke** andere aandoeningen gaat het (max. 3)?

- 1
- 2
- 3

36 Deze patiënt heeft waarschijnlijk geen PAV. Hoe ziet uw **differentiaaldiagnose** er uit (max. 3)?

- 1
- 2
- 3

Deze kolom
niet invullen

4								1-7	8

									9
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									10
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									11
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									12
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									13
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									14-17
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									18-21
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									22-25
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									26-29
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									30-33
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									34-37
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Voor weergave resultaten Doppler-onderzoek, zie formulier
"Enkel-Arm-Index; Eerste Doppler-Meting".

Enkel-Arm-Index; Eerste Doppler-Meting

5

Deze kolom
niet invullen

Lees eerst de instructie.

Datum-19.....

Onderzoeksnummer

1 Doppler-meting uitgevoerd door:

☐1 praktijkassistente; naam:

☐2 collega-arts; naam:

☐3 huisarts die L.O.
verricht heeft; naam:

☐

38

2 Systolische druk arm

a Links

b Rechts

--	--	--

39-41

--	--	--

42-44

3 Systolische druk enkel

a Links

b Rechts

--	--	--

45-47

--	--	--

48-50

4 Index

a linker-enkel-druk

hoogste arm-druk = ☐1 < 95% ☐2 ≥ 95%

☐

51

b rechter-enkel-druk

hoogste arm-druk = ☐1 < 95% ☐2 ≥ 95%

☐

52

Indien minimaal een van beide indexen kleiner is dan 95%, wordt een afspraak gemaakt voor een 2e meting, 1 week later (Zie formulier "Enkel-Arm-Index; Tweede Doppler-Meting").

Indien beide indexen groter dan of gelijk zijn aan 95%, beschouwen we de patiënt als niet lijdend aan PAV. Hij/zij komt niet in aanmerking voor het interventieonderzoek.

HARTELIJK DANK VOOR UW MEDEWERKING

Enkel-Arm-Index; Tweede Doppler-Meting

Deze kolom
niet invullen

Lees eerst de instructie.

Datum-19.....

Onderzoeksnummer

5 Doppler-meting uitgevoerd door:

- ☐1 praktijkassistente; naam:
- ☐2 collega-arts; naam:
- ☐3 huisarts die L.O. verricht heeft; naam:

☐ 53

6 Systolische druk arm

a Links

b Rechts

☐ ☐ ☐ 54-56

☐ ☐ ☐ 57-59

7 Systolische druk enkel

a Links

b Rechts

☐ ☐ ☐ 60-62

☐ ☐ ☐ 63-65

8 Index

a linker-enkel-druk

hoogste arm-druk = ☐1 < 95% ☐2 ≥ 95%

☐ 66

b rechter-enkel-druk

hoogste arm-druk = ☐1 < 95% ☐2 ≥ 95%

☐ 67

Indien minimaal **een van beide** E-A-indexen ook nu **kleiner** is dan 95%, dan beschouwen we de patiënt als lijdend aan PAV. De patiënt komt dan in aanmerking voor opname in het interventie-onderzoek.

Indien de **laagste** E-A-index **gelijk is aan of groter is** dan 95%, beschouwen we de patiënt als **niet** lijdend aan PAV. De patiënt komt dan niet in aanmerking voor opname in het interventie-onderzoek.

De **hulsarts** die de patiënt klinisch onderzocht heeft, dient nu de vraag op de volgende pagina te beantwoorden:

Evaluatie

7

Deze kolom
niet invullen

Datum

.....-.....-19.....

Onderzoeksnummer

.....

Volgens de criteria die we in het PAV-project Limburg gebruiken, heeft deze patiënt PAV, in meer of minder ernstige vorm.

9 Geef aan, wat voor u geldt in relatie tot deze patiënt:

- ☐1 deze patiënt was (mij) **bekend** met PAV
- ☐2 deze patiënt was **niet bekend** met PAV, maar ik **verwachtte het wel** op basis van mijn klinische diagnostiek in het kader van dit onderzoek
- ☐3 deze patiënt was **niet bekend** met PAV, en ik had het ook **niet verwacht**, gezien de resultaten van mijn klinische diagnostiek in het kader van dit onderzoek.

68

HARTELIJK DANK VOOR UW MEDEWERKING

Appendix 5.4 Commentary on registration forms & variables

PATIENT QUESTIONNAIRE

Date of completion and date of birth: age influences the atherosclerotic process, and therefore possibly also complaints, physical diagnosis and AB-ratio.

The age of the patient at completion of the postal questionnaire is the difference between the date of completion of the questionnaire ('questionnaire date') and the date of birth of the patient. The number of days of difference was divided by 365.25 in order to obtain the age in years. In case the questionnaire date was missing or the patient did not respond, the reference date taken was the median date of the period within which the postal inquiry was completed in the practice concerned. These data were necessary to demonstrate whether the responders formed an age-dependent selection of the total population.

The patients were older at the time they were examined in the practice. The 'age at examination' is the difference between the date on which the patient was examined ('date of examination') and the date of birth. The number of days of difference was divided by 365.25 to obtain the age in years. In case the date of examination was missing or the patient did not participate, the reference date taken was the median date of the period within which the examinations took place in the practice concerned. These data were necessary to demonstrate whether the participants formed an age-dependent selection of the population invited for examination.

The difference between the age at examination and the age at postal inquiry was due to the processing of the results of the postal inquiry and the final modification of the registration forms for the examination ('investigation delay'). This shift of the age distribution to higher ages has implications for the categorization of the age distribution in the study population: the youngest age category (40-45) decreased whereas the oldest category (>75) increased in number.

Gender: gender influences the atherosclerotic process, and therefore possibly also complaints, physical diagnosis, and AB-ratio.

Occupation: important to obtain a global impression of the social status of the patient (analysis of risk factors), and to help assess the answers provided to the questions on physical exercise.

Questions 1 and 2, complaints while walking. These are the crucial opening questions: does the patient possibly have claudication or not?

Questions 3 to 7: a specification of complaints while walking in terms of character and location. Not only are pain and cramps enquired after, but also less classic sensations and locations of complaints in the leg. Question 7 offers the respondent the opportunity to indicate an aspecific complaint. These variables can possibly refine the clinical diagnosis.

Questions 8 to 11: the influence of behaviour on the complaint. The purpose of these questions is to assess the probability of the patient having claudication. In questions 9 to 11, 5- or 6-point scales are used in order to ascertain whether less classic pain patterns occur.

Questions 12 to 14: influence of the walking complaints on daily life. These questions are intended to yield a view as to what extent the patient is encumbered by his leg complaints in social activities. In order to have the patient make a clear choice, a 4-point scale was selected here. These questions may yield data that could make it worthwhile to evaluate more closely the social consequences of intermittent claudication.

Questions 15 to 19: complaints at rest. These questions deal with complaints at night, both of possible claudicants and of non-claudicants. Question 18 is an open question, so that less classic complaints may be reported also. Question 19 is a 'test question': in classic PAOD the patient should have less complaints on suspending the leg outside the bed.

Questions 20 to 23: cold feet. The literature is equivocal in its judgement as to whether cold feet are a symptom of PAOD or not. The trend seemed to be: 'no, unless the complaint developed recently and is unilateral'.

Question 24: erection problems. This question is considered important for the evaluation of the extent and consequences of PAOD. A pilot study among patients indicated that there were no major objections to this question.

Questions 25 to 29: some differential diagnostic questions. Sitting, standing, or bending backwards should not give complaints in classical PAOD, in contrast to cycling and running. The answers may indicate to what extent other disorders possibly (also) contribute to the complaints of the patient, such as osteoarthritis, venous insufficiency, spinal stenosis, etc.

Questions 30 to 32: smoking. This is an important risk factor. Presumably, the data provided by the patient himself are more reliable and complete than those of the general practitioner.

Question 33: atherosclerosis in the family. A risk factor of which the patient possibly has a different view than the general practitioner.

Question 34: self-medication. The goal of this question is to identify the use of salicylic acid derivatives. This could influence both the pattern of complaints and the AB-ratio.

Questions 35 to 37: physical exercise. The purpose of these questions was to gain a global view of the extent of physical exercise of the patient. Much exercise may have a protective influence, while little exercise may have a masking effect. Much exercise also can have a provoking effect on complaints. Depending on the outcome, a more detailed study in this area could be worthwhile.

THE GENERAL PRACTITIONER'S FORM

The physical examination (items 1-18) was carried out by the general practitioner according to protocol.

Items 1 to 8: general: obesity (burden for the legs, risk factor?) and a number of basic vascular data

Items 9 to 13: inspection for trophic skin changes. There is no consensus in the literature on the significance of the pattern of hair growth, ulcers, and the skin colour of the legs in relation to PAOD.

Items 14 to 18: peripheral pulsations. The palpation of peripheral arterial pulsations, as well as the auscultation of the femoral arteries, are traditional aspects of the physical examination. Nonetheless, the literature gives reason to doubt the significance of these procedures with regard to diagnosing PAOD.

The dependency test of Ratschow-Bürger was not investigated. Considering that this test is presumably only rarely applied in general practice, and that its inclusion in the study would have demanded extra time from the general practitioners, it was decided not to examine this variable.

Data from the patient record (items 19 to 33) were copied onto the registration forms by the general practitioner.

Items 19 to 28: risk factors. Concerned were risk factors as they were known to the general practitioner. In view of the present uncertainties in the literature one might have wished, in hindsight, that serum cholesterol (and triglyceride) levels were also assessed. The reasons for not including these assessments were the following:

- the primary purpose of including items 19 to 28 was to establish in how far data from the patient record — i.e. risk factors known to the general practitioner — can contribute to the general practitioner's diagnostic judgement
- a higher drop-out rate was expected if the patients were to be subjected to an invasive test (in hospital or health centre)

Items 29 to 33: exclusion criteria for the 'course & intervention study'.

- vascular surgery (items 29 to 33)
- use of salicylic acid derivatives and oral anticoagulants (item 33)

Item 33: vaso-active medication. Item 33 also served to establish which drugs the patient uses. Especially important are ergotamine preparations, beta-blockers, calcium antagonists, and other

vasodilators. These could be confounding variables with respect to the pattern of complaints and the AB-ratio.

Clinical diagnosis, differential diagnosis, and other leg problems (items 34 to 36):

Clinical diagnosis and differential diagnosis: here the general practitioner gave his own opinion on the patient, based on the pattern of complaints (questionnaire), the findings of the physical examination, and the data from the patient record, against the background of his knowledge of the patient and of the latter's (illness) behaviour. It was considered important to compare the summational judgement of the general practitioner with the diagnostic models resulting from the multivariable analysis.

Other leg complaints: in order to identify diagnostic relationships in the study population, it is essential to know what effect the selection process had on disorders other than PAOD which can cause leg complaints. Moreover, the extent of the PAOD problem can thus be compared to the extent of other leg problems in the study population. The 'other leg complaints' were categorized as follows:

- Raynaud's disease, Brger's disease, chilblained feet
- varicose veins, venous insufficiency, venous ulcer
- osteoarthritis hip, knee, ankle, leg n.o.s
- peripheral neuropathy, lumbar disc lesion, sciatic pain, neuralgia
- restless legs, paraesthesia, muscular cramps
- pain and other complaints of legs n.o.d.
- no leg problems

Evaluation: filled in by the general practitioner after the AB-ratio was assessed. For each patient considered to have PAOD on the basis of two consecutive AB-ratio measurements yielding <0.95, the general practitioner had to indicate whether the subject was already known as such. The literature suggests that there are many unknown patients with PAOD.

Appendix Chapter 6 Additional tables

Abbreviations: S source population, R responders (postal inquiry), NR non-responders, I invited population, P participants, study population, NP non-participants

Appendix 6.1 Age distribution in the source, response and non-response population

	S	R	NR
Total	26620	23004	3616
Missing _{age}	975	66	909
N	25654	22938	2707
Range (yr)	40.3 - 76.9	40.3 - 76.9	40.3 - 76.7
SD (yr)	9.8	9.8	10.0
Mean (yr)	56.5	56.5	56.5
Median (yr)	56.1	56.1	56.0

Appendix 6.2 Proportion of non-responders in different age-categories

Age category	S	NR	%NR	95%CI _{%NR}
40 ≤ 45	3989	424	10.6	9.67-11.6
45 ≤ 55	7919	852	10.7	10.1-11.4
55 ≤ 65	7915	797	10.1	9.41-10.7
65 ≤ 75	5266	556	10.6	9.73-11.4
> 75	556	79	14.2	11.3-17.1
N	25645	2707	10.6	10.2-10.9

p = 0.0377

Appendix 6.3a Distribution of gender in the source, response and non-response population. Crude data.

	S	R	NR
Total	26620	23004	3616
Missing _{gender}	18	18	0
N (%)	26602 (100.0)	22986 (100.0)	3616 (100.0)
Male (%)	12563 (47.2)	10911 (47.5)	1652 (45.7)
Female (%)	13866 (52.1)	12075 (52.5)	1791 (49.5)
Unknown (%)	173 (0.7)	0 (0)	173 (4.8)

When the data on gender that were either not filled in (18) or unknown (173) would be divided according to the observed gender distribution in S, the result would be 91 men and 100 women. These figures are incorporated in appendix 6.3b, in which the 95% confidence intervals of the percentages are also given.

Appendix 6.3b Distribution of gender in the source, response and non-response-population. Data adjusted for 'missing' and 'unknown'

	S	R	NR
Male (%)	12654 (47.5)	10920 (47.5)	1734 (48.0)
- 95%CI _{%male}	46.9-48.1	46.9-48.1	46.4-49.6
Female (%)	13966 (52.5)	12084 (52.5)	1882 (52.0)
- 95%CI _{%female}	51.9-53.1	51.9-53.1	50.4-53.6
Total (%)	26620 (100.0)	23004 (100.0)	3616 (100.0)

p = 0.588

Appendix 6.4 Proportion of non-responders by gender. Based on table 6.3b.

Gender	% NR	95%-confidence interval
Male	13.7	13.1 - 14.3
Female	13.5	12.9 - 14.1
Total	13.6	13.2 - 14.0

Appendix 6.5 Representativeness, for age and gender, of both random samples from the response population

Category		I, group 1	R, score 0	Sample fraction I1/R0 (%)	I, group 2	R, score 1-5	Sample fraction I2/R1-5 (%)
<i>Age</i>	40 ≤ 45	94	1778	5.29	118	1787	6.60
	45 ≤ 55	137	2997	4.57	248	4071	6.09
	55 ≤ 65	132	2666	4.95	296	4452	6.65
	65 ≤ 75	81	1491	5.43	214	3219	6.65
	> 75	6	124	4.84	18	353	5.10
<i>N_{age}</i>		450	9056	4.97	894	13882	6.44
<i>Missing_{age}</i>		1	39		3	27	
<i>Gender</i>	Male	206	4282	4.81	412	6629	6.22
	Female	245	4807	5.10	485	7268	6.67
<i>N_{gender}</i>		451	9089	4.96	897	13897	6.45
<i>Missing_{gender}</i>		0	6		0	12	

Pearson chi-squares: age: sample I1/R0: $p = 0.706$, sample I2/R1-5: $p = 0.644$; gender: sample I1/R0: $p = 0.531$, sample I2/R1-5: $p = 0.272$

Appendix 6.6 Age distribution in the invited, study, and non-participant population (age at time of postal inquiry)

	I	P	NP
Total	5301	3654	1647
<i>Missing_{age}</i>	6	0	6
<i>N</i>	5295	3654	1641
Range (yr)	40.3 - 76.9	40.3 - 76.9	40.5 - 76.8
SD (yr)	9.8	9.6	10.2
Mean (yr)	58.7	58.1	60.0
- 95%CI _{mean}	58.4 - 59.0	57.8 - 58.4	59.5 - 60.5
Median (yr)	59.1	58.3	61.1

Appendix 6.7 Proportion of non-participants in different age-categories (age at time of postal inquiry) of the invited population

Age category	I	NP	%NP	95%CI _{%NP}
40 ≤ 45	594	178	30.0	26.3-33.7
45 ≤ 55	1387	371	26.7	24.4-29.1
55 ≤ 65	1713	464	27.1	25.0-29.2
65 ≤ 75	1436	553	38.5	36.0-41.0
> 75	165	75	45.5	37.9-51.1
<i>N</i>	5295	1641	31.0	29.7-32.2

$p < 0.0001$.

Appendix 6.8 Distribution of gender in the invited, study, and non-participant population

	I	P	NP
Total	5301	3654	1647
Missing _{gender}	2	0	2
N (%)	5299 (100.0)	3654 (100.0)	1645 (100.0)
Male (%)	2535 (47.8)	1719 (47.0)	816 (49.6)
- 95%CI _{%male}	46.5-49.1	45.4-48.6	47.2-52.0
Female (%)	2764 (52.5)	1935 (53.0)	829 (50.4)
- 95%CI _{%female}	50.9-53.5	51.4-54.6	48.0-52.8

p= 0.084

Appendix 6.9 Proportion of non-participants by gender

Gender	% NP	95% confidence interval
Male	32.2	30.4 - 34.0
Female	30.0	28.3 - 31.7
N	31.1	29.9 - 32.3

Appendix 6.10 Distribution of 'score' in the invited, study, and non-participant population and proportion of non-participants in each category of 'score'.

Score	I	P	NP	%NP	95%CI _{%NP}
0	451	292	159	35.3	30.8-39.7
1	562	389	173	30.8	27.0-34.6
2	2614	1869	745	28.5	26.8-30.2
3	1166	776	390	33.4	30.7-36.2
4	384	244	140	36.5	31.6-41.3
5	124	84	40	32.3	24.0-40.5
Total	5301	3654	1647	31.1	29.8-32.3

p= 0.0012

Appendix 6.11 Distribution of 'group' in the invited, study, and non-participant population and proportion of non-participants in each category of 'group'.

Group	I	P	NP	%NP	95%CI _{%NP}
1 ('no risk')	451	292	159	35.3	30.8-39.7
2 ('increased risk')	897	626	271	30.2	27.2-33.2
3 ('high risk')	3953	2736	1217	30.8	29.3-32.2
Total	5301	3654	1647	31.1	29.8-32.3

p= 0.126.

Appendix Chapter 8 Comparison of ROC-curves (for the GPC AB-ratio): confidence intervals, optimum cutoff values.

Arnold DM Kester, Henri EJH Stoffers

A 95% confidence interval for the optimal cutoff value was obtained by testing for each possible cutoff value the hypothesis that there is no difference in validity (= the sum of sensitivity and specificity) between the optimum cutoff value and that specific cutoff value (chi-square test). The most extreme values for which the hypothesis was not rejected were taken as the limits of the interval.

The equality of the optimum cutoff values in the ROC curves of both sexes was analyzed by testing this hypothesis in the 'male' and in the 'female' curve; the tests were combined using the Mantel-Haenszel technique. The difference was non-significant ($p=0.3$). The equality of the maximum validity in both curves was tested by division of the difference of the estimated maximum validities by the estimated s.e. of that difference ($p=0.27$).

Parametric comparison of ROC curves is usually done under the assumption of a normal distribution in both groups, possibly after a suitable transformation.¹ However, in our data a satisfactory fit to the raw curve was not obtained that way. Therefore the ROC curve was smoothed. Using logistic regression the probability of PAOD at each value X for the AB-ratio was estimated. The formula gives these probabilities assuming estimated parameters a and b from a linear logistic model:

$$\text{Prob}(PAOD|X) = \frac{\exp(a + b \cdot X)}{1 + \exp(a + b \cdot X)}$$

Subsequently, the sensitivity and specificity at each possible cutoff C according to this model are calculated as

$$\text{sens}_{\text{model}}(C) = \frac{\sum_{X \leq C} \text{Prob}(PAOD|X)}{\sum \text{Prob}(PAOD|X)} \quad \text{and} \quad \text{spec}_{\text{model}}(C) = \frac{\sum_{X > C} 1 - \text{Prob}(PAOD|X)}{\sum 1 - \text{Prob}(PAOD|X)}$$

The smoothed ROC curve was obtained by plotting $\text{sens}_{\text{model}}$ against $1 - \text{spec}_{\text{model}}$. Using a third degree logistic model for the probabilities, a close fit was obtained. For the means of 3 consecutive AB-ratio measurements, a linear logistic model was used.

For each of these techniques a method was used which allowed for the dependence of left and right legs of each patient (generalized estimating equations).^{2,3,4} The correlation coefficient of left and right legs was approximately 0.35.

References

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Appendix Chapter 9 Recalculation of prevalence figures for the base population (example of a spreadsheet; formulas)

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Example

PREVALENCE PAOD (AB-RATIO<0.95) , MEN & WOMEN, ALL AGES

agecat	score	study_n _i	resp_N _i	PAOD	P _i	var(P _i)	ci_L(P _i)	ci_R(P _i)	C _i	P	Var(P)	ci_L(P)	ci_R(P)
4555	0	92	2996	1	0.010869	0.000116	-0.01031	0.032057	0.424122				
4555	1	133	2604	2	0.015037	0.000111	-0.00564	0.035721	0.368629				
4555	2	513	1059	28	0.054580	0.000100	0.034923	0.074238	0.149915				
4555	3	173	285	20	0.115606	0.000590	0.067958	0.163255	0.040345				
4555	4	50	89	5	0.1	0.0018	0.016844	0.183155	0.012599				
4555	5	20	31	0	0	0	0	0	0.004388				
5565	0	93	2665	2	0.021505	0.000226	-0.00797	0.050988	0.374508				
5565	1	128	2520	11	0.085937	0.000613	0.037382	0.134492	0.354131				
5565	2	634	1338	69	0.108832	0.000152	0.084590	0.133074	0.188026				
5565	3	269	410	49	0.182156	0.000553	0.136031	0.228281	0.057616				
5565	4	95	145	15	0.157894	0.001399	0.084568	0.231221	0.020376				
5565	5	30	38	2	0.066666	0.002074	-0.02259	0.155928	0.005340				
6575	0	44	1488	2	0.045454	0.000986	-0.01609	0.107002	0.316326				
6575	1	72	1585	9	0.125	0.001519	0.048607	0.201392	0.336947				
6575	2	479	1057	101	0.210855	0.000347	0.174325	0.247386	0.224702				
6575	3	255	407	63	0.247058	0.000729	0.194120	0.299896	0.086522				
6575	4	71	129	23	0.323943	0.003084	0.215087	0.432799	0.027423				
6575	5	18	38	1	0.055555	0.002914	-0.05026	0.161376	0.008078				
all ages	0	229	7149	5	0.021834	0.000093	0.0023905	0.040762	0.378574				
all ages	1	333	6709	22	0.066066	0.000185	0.039386	0.092745	0.355274				
all ages	2	1626	3454	158	0.121771	0.000065	0.105875	0.137666	0.182906				
all ages	3	697	1102	132	0.189383	0.000220	0.160294	0.218471	0.058356				
all ages	4	216	363	43	0.199074	0.000738	0.145822	0.252325	0.019222				
all ages	5	68	107	3	0.044117	0.000620	-0.00469	0.092927	0.005666				

0.024259 0.000039 0.011916 0.036603
0.073019 0.000116 0.051856 0.094182
0.134585 0.000236 0.100827 0.168343
0.069138 0.000039 0.056742 0.081534

Formulas

score	prior risk score on postal inquiry
study n_i	number of subjects with a specific score in the study population
resp N_i	number of subjects with a specific score in the base population
PAOD	number of patients with variable of interest (here: PAOD) in the study population
p_i	prevalence of variable in each category of 'score' in the study population = $(PAOD/n_i)$
$var(p_i)$	variance of $p_i = \{PAOD \times (n_i - PAOD)\} / n_i^3$
$ci_L(p_i)$	left side of 95% confidence interval for $p_i = p_i - 1.96\sqrt{var(p_i)}$
$ci_R(p_i)$	right side of 95% confidence interval for $p_i = p_i + 1.96\sqrt{var(p_i)}$
C_i	= $N_i / \Sigma N_i$
P	prevalence of variable in the base population = $\Sigma(C_i \times p_i)$
$Var(P)$	variance of P = $\Sigma(C_i^2 \times var(p_i))$
$ci_L(P)$	left side of 95% confidence interval for P = $P - 1.96\sqrt{Var(P)}$
$ci_R(P)$	right side of 95% confidence interval for P = $P + 1.96\sqrt{Var(P)}$

Appendix Chapter 10 Calculation of the predicted probability of PAOD using the multivariable logistic regression models

The probability of PAOD being present can be estimated according to the formula

$$P = 1 / \{1 + e^{-g}\}$$

where $g = (a + b_1 \times x_1 + b_2 \times x_2 + \dots b_i \times x_i)$, a is the coefficient of the constant in the model, and b_1, b_2, b_i are the coefficients of the variables in the model.

For our most comprehensive model (4) the coefficients are given in *table 10.4*. The values of the x_i s is 0 if the test has a negative (normal) outcome, and 1 if the test has a positive (abnormal) outcome. Below the calculations are given for the examples given in the section 'Results' of *chapter 10* (model 4).

Example 1: a woman, 62 years old, with intermittent claudication, abnormal pedal pulses, and all other 'tests' negative has a probability of

$$1 / \{1 + e^{-(-5.06 + 0.78 + 1.18 + 2.55)}\} = 0.37$$

to have PAOD in this leg.

Example 2: a man, 75 years old, with intermittent claudication, abnormal pedal pulses, a femoral bruit, who smokes and other tests negative, has a probability of

$$1 / \{1 + e^{-(-5.06 + 0.25 + 0.78 + 1.18 + 2.55 + 1.40 + 0.80)}\} = 0.87$$

to have PAOD in this leg.

In the same way less differentiated predictions can be made using the less extensive models (1-3). The coefficients of these models can be recalculated from the odds ratios (OR), using the formula

$$b_i = \ln(OR_i)$$

where $\ln$ is the natural logarithm.