The prognosis of non-critical limb ischaemia: a systematic review of population-based evidence

JURENNE D HOOI

HENRI E J H STOFFERS

J ANDRÉ KNOTTNERUS

JAN W VAN REE

SUMMARY

Background. *Peripheral arterial occlusive disease (PAOD) is the most common peripheral vascular disorder in the elderly. A clear picture of the disease's course, especially in patients with non-critical limb ischaemia (Fontaine stages I and II), is essential for the general practitioner, who plays a key role in the diagnosis and management of PAOD.*

Aim. *To evaluate the population-based evidence on the course and prognosis of PAOD.*

Methods. *An exhaustive literature search yielded 16 population-based studies on the prognosis of PAOD. The methodological qualities of the studies were assessed according to eight criteria.*

Results. *Thirteen studies of high methodological quality show that data on the course, cardiovascular morbidity, and mortality of asymptomatic PAOD are scarce. Only a small group of asymptomatic patients seem to develop intermittent claudication symptoms. However, asymptomatic patients appear to have the same increased risk for cardiovascular morbidity and mortality when compared with claudicants. No data were available on prognostic factors for intermittent claudication and cardiovascular morbidity in asymptomatic patients. The course, cardiovascular morbidity, and mortality of symptomatic PAOD are better documented. A small group of claudicants experience symptom progression. Smoking, hypertension, increasing age, and diabetes are the most relevant risk factors for intermittent claudication. Claudicants are at a higher risk for developing other cardiovascular diseases, resulting in a significantly increased mortality mainly owing to coronary heart disease. Intermittent claudication and a low ankle-brachial pressure index are significant predictors of mortality. Men had intermittent claudication and symptom progression more often than women. Cardiovascular (co-)morbidity was common in both male and female PAOD patients, but male PAOD patients had a higher mortality compared with female PAOD patients.*

Conclusion. *Given the current knowledge on the prognosis of PAOD in the general population, an important task for (secondary) prevention is reserved for the general practitioner. Further research is required to document the course and prognosis of asymptomatic PAOD patients.*

Keywords: peripheral arterial occlusive disease; epidemiology; prognosis.

J D Hooi, MSc; H E J H Stoffers, MD, PhD; J A Knottnerus, professor of family practice; and J W van Ree, professor of family practice, Department of General Practice, Extramural and Transmural Health Care, Maastricht University, Maastricht, The Netherlands.
Submitted: 23 September 1997; final acceptance: 15 June 1998.

Introduction

PERIPHERAL arterial occlusive disease (PAOD) is a common health problem among the elderly.[1] The prevalence of PAOD in the general population, assessed by means of the ankle-brachial pressure index, ranges from 4.2% to 35%.[2-4]

The majority of PAOD patients have asymptomatic PAOD (Fontaine stage I) or intermittent claudication symptoms (stage II). Intermittent claudication can be physically disabling and claudicants have a diminished quality of life because of the impact of their symptoms on their daily life activities.[5] In a small group of PAOD patients, symptoms are continuously present (stage III) and a small minority experience gangrene and/or necrosis (stage IV). Stages I and II are denoted as non-critical limb ischaemia and stage III and IV as critical limb ischaemia.[6]

Much research has been done on the prognosis of PAOD in referred patients with disabling claudication complaints or critical ischaemia.[7-17] However, these referral-based studies are not representative for PAOD patients in primary care, since, in this setting, the majority of patients have non-critical limb ischaemia. Data from population-based studies can provide the general practitioner (GP) with valuable information; for example, which factors are of prognostic importance in the clinical course of asymptomatic and mildly symptomatic PAOD? Do patients with non-critical limb ischaemia have advanced atherosclerosis in other parts of the circulation more often, resulting in an increased risk for cardiovascular morbidity and mortality? Is PAOD a predominantly male disease? And to what extent is the knowledge on these issues based on results of methodologically well-designed epidemiological studies? In order to answer these questions, we present a systematic review of methodologically well-designed population-based studies on the prognosis of non-critical ischaemia.

Method

Identification and selection procedure

A MEDLINE literature search of the period between 1980 and 1996 was conducted using the following keywords: 'peripheral occlusive disease', 'peripheral arterial disease', 'peripheral vascular disease', 'atherosclerosis', 'intermittent claudication', 'epidemiology', 'prognosis', 'ankle-brachial pressure index', 'prospective', 'follow-up', 'morbidity', 'mortality', 'not surgery', and 'not clinical trial'. Studies were selected if they were population-based and primarily aimed to investigate prognosis, with at least one year of follow-up. References cited in these studies were screened for additional relevant publications.

Assessment of methodological quality

To evaluate the methodological quality of the selected papers, a set of eight criteria was formulated according to Tugwell and Silagy:[18,19]

1. clear description of the study population,
2. clearly defined diagnosis of PAOD,
3. baseline measurements for all subjects,
4. documentation of follow-up length,
5. less than 20% loss to follow-up,
6. documentation of measurements of prognostic factors,

7. documentation of end points, and
8. adequate statistical methods.

The scoring categories for each item were: + (present), ± (questionable), and – (absent). The questionable score was assigned if a criterion was incompletely specified. When no information was present a negative score was given.

The selected papers were independently reviewed by JDH and HEJH. The results were compared and disagreements were discussed until consensus was reached. Studies were included in this review if they had no more than one questionable or negative criterion.

Results

General remarks

The literature search resulted in the identification of 19 population-based studies.[20-38] Four sets of papers reported on the same populations. Consequently, in some papers, the results overlapped or were complementary. In one set of three papers,[34-36] the two papers with the longest follow-up period with complementary data were selected.[35,36] In a second set of three papers,[27-29] the paper that included the most accurate information on the prognosis of PAOD was chosen.[28] The third (four papers)[30-33] and fourth set (two papers)[37-38] were fully presented in the methodological quality assessment, because each paper contained additional data. Thus, 16 papers were selected for the methodological assessment.

Methodological quality assessment

Table 1 describes the methodological qualities of the 16 papers. Thirteen papers met our inclusion condition. In the older papers, loss to follow-up (criterion 5) and measurements of prognostic factors (criterion 6) were often not accurately documented. Older papers also applied fewer adequate statistical analyses (criterion 8).

Study populations and diagnostic measurements

Table 2 reviews the study populations and diagnostic measurements of the 13 papers. The 13 study populations in fact consisted of nine cohorts, with age ranging from 29 to 93 years. In four cohorts, cases were defined by the presence of intermittent claudication, measured using the WHO questionnaire.[39,40] In the other five studies, ankle-brachial pressure index was included in the case definition.[41,42] An ankle-brachial pressure ≤0.90 was considered indicative for PAOD in three of these five studies. The other two studies used a variety of non-invasive measurements including an ankle-brachial pressure index ≤0.90 or ≤0.80 as case definition.

Cardiovascular mortality

Table 2 also summarizes the data on the mortality of PAOD. Most of the total mortality could be attributed to cardiovascular death. Four studies presented the mean follow-up period.[20,21,24,28] From these studies, the person-years at risk were retrievable and the crude total and cardiovascular mortality rates calculated. The crude total mortality rate ranged from 0.9 to 6.4 per 100 person-years at risk.[20,21,24,28] The crude cardiovascular mortality rate ranged from 0.7 to 2.8 per 100 person-years at risk.[20,21,24,28] The adjusted relative risks of total, cardiovascular, and coronary heart disease mortality were significantly elevated in claudicants, even when these patients were free of a history of cardiovascular disease at baseline (Table 3). When the ankle-brachial pressure index was included in the case definition, PAOD patients had an even greater risk for cardiovascular mortality. Statistical pooling of the relative risks was not feasible because of the heterogeneity of the study populations.

Both the Belgian study and the Edinburgh Artery study showed a trend of an increased total and cardiovascular mortality in asymptomatic PAOD patients.[25,38] Asymptomatic PAOD was associated with significantly elevated cardiovascular mortality risks, even when these patients had no history of cardiovascular disease at baseline (Table 3).

All but two studies confirmed any intermittent claudication, an ankle-brachial pressure index ≤0.90, or other abnormal non-invasive test results as significantly independent prognostic factors for cardiovascular death in PAOD patients.

Only the Whitehall study and the Edinburgh Artery study reported on cerebrovascular death. Cerebrovascular death was less common than coronary death, but was still elevated in PAOD patients.

The clinical course of symptomatic and asymptomatic PAOD

Table 4 summarizes risk factors and clinical course of PAOD. Increasing age, smoking, diabetes, and hypertension were risk factors for the development of intermittent claudication in the Framingham and the Quebec Vascular studies.[21,33] The contribution of smoking was the strongest, increasing the risk from two to four times. In the Framingham study, high serum cholesterol was also a risk factor for claudication, but this was not confirmed by the Quebec Vascular study. In the Framingham study, after a mean of 8.5 years, seven (4.3%) of the 162 claudicants experienced symptom progression resulting in amputations. Of these, five were diabetic and three were smokers. In the Edinburgh Artery study, after five years, seven (9.6%) of the 73 claudicants had symptom deterioration, resulting in critical ischaemia, amputation, and/or vascular surgery.[38]

Table 1. Methodological scores of the studies on the prognosis of PAOD.

	Criteria							
Author[a]	1	2	3	4	5	6	7	8
Widmer, 1964[26]	+	+	+	+	±	±	±	±
Kannel, 1970[30]	+	+	+	+	+	+	+	±
Newton Peabody, 1974[31]	+	+	+	+	+	+	+	–
Agner, 1981[23]	+	+	+	+	–	±	+	±
Reunanen, 1982[22]	+	+	+	+	–	+	+	+
Kannel, 1985[32]	+	+	+	+	+	±	+	±
Stokes, 1987[33]	+	+	+	+	-	+	+	+
Davey Smith, 1990[20]	+	+	+	++	+	+	+	+
Criqui, 1991[35]	+	+	+	±	+	+	+	+
Dagenais, 1991[21]	+	+	+	++	+	+	+	+
Criqui, 1992[36]	+	+	+	–	+	+	+	+
Ögren, 1993[28]	+	+	+	++	+	+	+	+
Vogt, 1993[24]	+	+	+	++	+	+	+	+
Kornitzer, 1995[25]	+	+	+	+	+	±	+	+
Leng, 1996[37]	+	+	+	+	+	+	+	+
Leng, 1996[38]	+	+	+	+	+	+	+	+

++ Criterion is specified and the mean follow-up duration was stated in the papers; + present; – absent; ± questionable. [a]Name of first author listed only. Criteria: (1) clear description of the study population; (2) clearly defined diagnosis of PAOD; (3) baseline measurement for all subjects; (4) documentation of follow-up length; (5) loss to follow-up not more than 20%; (6) documentation of measurements of prognostic factors; (7) documentation of end points; (8) adequate statistical methods.

Table 2. Mortality in patients with peripheral arterial occlusive disease (PAOD). Results from nine population studies. (IC = intermittent claudication; ABPI = Ankle-brachial pressure index.)

Studies (Author)[a]	Study population (age and sex)	Diagnostic criteria	PAOD subjects male/female	Follow-up period as stated in papers (years)	Total mortality male/female	Total mortality rate	Cardiovascular (CVD) mortality male/female		CVD mortality rate	Prognostic factors for mortality
							CVD	CHD[b]		
Framingham study, 1970 (Kannel[30])	29–62 years 5209 men and women	IC questionnaire	79/46	14	23/8		16/8	–		IC
Helsinki study, 1982 (Reunanen[22])	30–59 years 5738 men 5224 women	IC questionnaire	122/93	5	18/2		15/-	7 –		smoking, CVD comorbidity
The Whitehall study, 1990 (Davey Smith[20])	40–64 years 18388 men	IC questionnaire	147[c] 175[d]	17[e]	56 70	2.2/100 2.4/100	45 42	–	1.8/100 1.4/100	IC
Quebec Vascular study, 1991 (Dagenais[21])	35–64 years 4570 men	IC questionnaire	188	12[e]	21	0.9/100	16	–	0.7/100	–
Lipid Research study, 1992 (Criqui[36])	38–82 years 256 men 309 women	A set of non-invasive criteria, including ABPI Û0.80 and IC questionnaire	34[f]/33[f]	10	21/11		16/6	12/3		PAOD
Malmö Sweden study, 1993 (Ögren[28])	68 years 477 men	ABPI <0.90 IC questionnaire	67[f]	7[e]	30	6.4/100	13	–	2.8/100	ABPI <0.90
Multicentre study of Osteoporotic Fractures, 1993 (Vogt[24])	65–93 years 1492 women	ABPI ≤0.90 IC questionnaire	–/82[f]	4.3[e]	–/18	5.1/100	–/10	–/5	2.8/100	ABPI ≤0.90
Belgian study, 1995 (Kornitzer[25])	40–55 years 2023 men	ABPI ≤0.90 and IC questionnaire	77[g]	10	8		4	4		Smoking, ABPI ≤0.90, low density lipoprotein cholesterol
Edinburgh Artery study, 1996 (Leng[37-38])	55–74 years 1592 men and women	A set of non-invasive criteria, including ABPI ≤0.90 and IC questionnaire	73[h] 105[i] 240[j]	5	14 32 33		10 12 20	4 7 12		ABPI ≤0.90

[a]Name of first author listed only; [b]coronary heart disease, as a subset of cardiovascular disease; [c]patients with probable IC; [d]patients with possible IC; [e]mean follow-up period; [f]asymptomatic PAOD patients included; [g]only asymptomatic PAOD patients; [h]claudicants; [i]major asymptomatic PAOD: ABPI ≤0.90 and drop in ankle pressure during reactive hyperaemia >20% or ABPI ≤0.70 or reactive hyperaemia >20%; [j]minor asymptomatic PAOD: ABPI ≤0.90 or reactive hyperaemia >20%.

Table 3. Adjusted relative risks (RR)[a] of total mortality, cardiovascular (CVD) mortality, and coronary heart disease (CHD) mortality for PAOD. Results from population-based studies. (ABPI = ankle-brachial pressure index.)

Studies (Author[b])		Total mortality RR (95% CI)	CVD mortality RR (95% CI)	CHD mortality RR (95% CI)
Framingham study, 1970 (Kannel[30])	RR for claudicants (male)	1.9	–	–
	RR for claudicants (female)	2.3	–	–
Helsinki study, 1982 (Reunanen[22])	RR for claudicants (male)	1.4 (P>0.05)	1.2 (P>0.05)	0.9 (P>0.05)
The Whitehall study, 1990 (Davey Smith[20])	RR for possible claudicants (male)	1.8 (1.5–2.4)	2.1 (1.5–2.8)	2.1 (1.4–3.0)
	RR for possible claudicants with no history of CVD at baseline (male)	2.4 (1.8–3.2)	2.8 (1.9–4.2)	2.8 (1.8–4.5)
	RR for probable claudicants (male)	1.7 (1.3–2.3)	2.7 (2.0–3.7)	2.9 (2.0–4.1)
	RR for probable claudicants with no history of CVD at baseline (male)	1.6 (1.1–2.3)	2.6 (1.7–4.0)	2.8 (1.8–4.5)
Lipid Research study, 1992 (Criqui[36])	RR for asymptomatic PAOD patients	2.7 (1.6–4.5)	4.7 (2.3–9.8)	5.6 (2.3–13.5)
	RR for asymptomatic PAOD patients with no history of CVD at baseline	2.6 (1.4–4.7)	5.1 (2.0–13.0)	3.1 (0.9–10.6)
	RR for claudicants	4.7 (2.3–9.6)	11.2 (4.5–27.9)	11.4 (3.6–35.8)
	RR for claudicants with no history of CVD at baseline	6.7 (2.5–17.6)	14.9 (3.8–58.2)	13.1 (2.5–67.6)
Malmö Sweden study, 1993 (Ögren[28])	RR for patients with an ABPI <0.90 (male)	2.3 (1.4–3.8)	–	2.6 (1.2–5.9)
Multicenter study of osteoporotic fractions, 1993 (Vogt[24])	RR for patients with an ABPI ≤0.90 (female)	3.1 (1.7–5.5)	4.0 (1.7–9.1)	3.7 (1.2–11.6)
	RR for patients with an ABPI ≤0.90, with no history of CVD at baseline (female)	3.1 (1.5–6.7)	4.5 (1.5–6.7)	–
Belgian study, 1995 (Kornitzer[25])	RR for asymptomatic patients (male)	2.8 (1.4–5.5)	4.2 (1.7–10.5)	5.0 (1.8–11.4)
Edinburgh artery study, 1996 (Leng[37,38])	RR for patients with an ABPI ≤0.90	1.6 (1.1–2.2)	1.9 (1.2–3.0)	1.9 (1.0 - 3.5)
	RR for claudicants	1.6 (0.9–2.8)	2.7 (1.3–5.3)	–
	RR for patients with major asymptomatic PAOD[c]	2.4 (1.6–3.7)	2.1 (1.1–3.8)	–
	RR for patients with minor asymptomatic PAOD[d]	1.2 (0.8–1.7)	1.7 (1.1–2.8)	–

[a]RR adjusted for other cardiovascular risk factors; [b]name of first author listed only; [c]major asymptomatic PAOD: ABPI = 0.90 and drop in ankle pressure during reactive hyperaemia >20% or ABPI ≤0.70 or reactive hyperaemia >20%; [d]minor asymptomatic PAOD: ABPI ≤0.90 or reactive hyperaemia >20%.

No data were available on risk factors for asymptomatic PAOD. In the Edinburgh Artery study, of the 345 asymptomatic PAOD patients, 33 (9.6%) developed intermittent claudication, and three (0.9%) underwent vascular surgery.[38] No data were available concerning prognostic factors that play a role in the transition of asymptomatic PAOD to symptomatic PAOD.

Cardiovascular morbidity

Table 4 also presents the proportion of cardiovascular morbidity in PAOD patients. Most cardiovascular morbidity was caused by coronary heart disease. The risk of non-fatal cardiovascular events increased with the duration of the follow-up period. In the Framingham study, 10 years after onset of intermittent claudication, more than 50% of the claudicants had developed cardiovascular diseases.[31] Claudicants from the Quebec study had a four-fold risk of developing a non-fatal ischaemic heart event as compared with the normal population.[21] In the Edinburgh Artery study, claudicants had a significantly increased risk for angina pectoris (relative risk [RR] = 2.3; 95% confidence interval [CI] = 1.04–5.10) as compared with the normal population.[38] In one study, an abnormal ankle-brachial pressure index was an important prognostic factor for non-fatal cardiovascular occurrences in PAOD patients.[37]

Only the Edinburgh artery study reported explicitly on the cardiovascular morbidity of asymptomatic PAOD patients.[38] They also had an increased risk of developing cardiovascular diseases. No data were available on prognostic factors for non-fatal cardiovascular events in asymptomatic PAOD patients.

Sex of subjects

Male subjects were present in eight of the nine cohorts, whereas female subjects were present in only five. Cumulative total mortality seemed more pronounced in male PAOD patients (up to 62%) as compared with female PAOD patients (up to 33%) (Table 2). Adjusted relative risks showed increased cardiovascular mortality in both sexes (Table 3).

Male PAOD patients were more likely to have intermittent claudication and unfavourable clinical course than female PAOD patients. In the Framingham study and the Lipid Research study, non-fatal events were more frequent in female PAOD patients than in male PAOD patients.[31,35]

Discussion

We found six papers that met all relevant methodological criteria, while a further seven had only one questionable or negative item. In general, recent studies were of better methodological quality than older studies. Nevertheless, the duration of the mean follow-up period, essential for the calculation of the person-years at risk for an event, was specified in only four studies.

In four studies, symptomatic PAOD was defined by means of the standardized WHO questionnaire on intermittent claudication. In five studies, the ankle-brachial pressure index was used as well. The WHO questionnaire is highly specific but only moderately sensitive.[41,43] Given the fact that, in the general population, asymptomatic PAOD is more common than symptomatic PAOD,[3,4] and that use of the WHO questionnaire does not reveal asymptomatic PAOD, its use in identifying patients at risk is less adequate. The ankle-brachial pressure index currently is the most common and widely applicable diagnostic method in epidemiologic studies, having a quite high sensitivity and a specificity of 95% or more.[1,3,41,42] It has a good reproducibility,[44] has a quantitative outcome, and is significantly associated with the severity of PAOD.[48]

The following conclusions can be drawn from this systematic

Table 4. Risk factors, clinical course, prognostic factors, and cardiovascular morbidity in patients with peripheral arterial occlusive disease (PAOD). Results from population-based studies.

	Claudicants	Asymptomatic PAOD patients
Risk factors	Increasing age,[21,33] smoking,[21,33] hypertension,[21,33] diabetes,[21,33] male sex,[21,33] high serum cholesterol[33]	No data
Proportion with symptom progression	4.3% (6 males; 1 female),[31] 9.6%[38]	10.4%[38]
Proportion with unfavourable outcome (surgery, amputation)	4.3% (6 males; 1 female),[31] 9.6%38	0.9%[38]
Prognostic factors for symptom progression	smoking,[31] diabetes mellitus[31]	No data
Proportion with cardiovascular morbidity	Incident cases in male and female: 29%[38] Incident cases male[a]: 5–56%[21,31,35] Incident cases female[a]: 16–66%[31,35] Prevalent cases male[a]: 15.4–29%[31,35] Prevalent cases female[a]: 16%[35]	Incident cases in male and female: 22.3%[38]

[a]Total PAOD group, including asymptomatic patients.

review of population-based data:

- Important risk factors for symptomatic PAOD are smoking, increasing age, hypertension, and diabetes.
- Claudicants do not often experience symptom progression with unfavourable outcomes unless smoking or diabetes are involved.
- Compared with asymptomatic PAOD patients and normal subjects, claudicants have a higher cardiovascular morbidity: mainly resulting from coronary heart diseases.
- Claudicants have an increased risk of cardiovascular death (main cause: coronary heart disease) compared with the general population.
- There is a lack of scientific data on the prognosis of asymptomatic PAOD. The data available indicate a relatively benign course as far as the legs are concerned. However, also in these patients, a trend of increased cardiovascular morbidity and mortality is observed.
- Strong independent predictors for cardiovascular mortality are intermittent claudication and an ankle-brachial pressure index ≤0.90 or other abnormal non-invasive test results.
- In women, PAOD seems to follow a more benign course as compared with men. The incidence of non-fatal cardiovascular events appears to be higher in female PAOD patients than in male PAOD patients. Increased mortality risks are observed in both sexes, but total mortality is higher in male PAOD patients.

Comparison with referral-based studies

Population-based evidence on risk factors, prevalence, and incidence and risk factors is more suitable for primary care than referral-based evidence. When comparing the results of this review with the evidence from referral-based studies, the following similarities emerge. Increasing age, smoking, and hypertension are the most significant risk factors, and smoking and diabetes are important prognostic determinants for symptom progression.[46,47] The proportion of cardiovascular death in referral-based and population-based studies is quite similar, and referred claudicants also have mortality risks two to five times higher than the general population.[48-50] The presence of intermittent claudication and an abnormal ankle-brachial pressure index (≤0.90) are strong independent predictors for cardiovascular mortality in referral-based PAOD cohorts.[11,13,16,48-50] Male referred claudicants have a higher total mortality compared with female referred PAOD patients,[45] the same trend that is observed in population-based studies.

However, there are also differences between population-based and referral-based studies. In referral-based studies, hypercholesterolaemia is mentioned as a risk factor,[46] whereas in population-based studies its role remains inconclusive. A much higher proportion of referred claudicants experience symptom progression (25%) and they have a higher prevalence of co-existing coronary and cerebrovascular disease (40–60%)[45-47] than claudicants from population-based studies (5–10% and 15–30%, respectively). Nevertheless, the reported incidences of non-fatal coronary and cerebrovascular disease in referral-based studies seem lower (19–35%)[45] compared with population-based studies (5–66%). Total mortality also seems to be higher in referred claudicants (5–80%)[45] compared with claudicants from population-based studies (2–62%).

Clinical implications

The GP has an important task in (secondary) prevention of cardiovascular diseases. With respect to PAOD, the preventive objectives are to avert symptom progression and to decrease cardiovascular morbidity and mortality.[51] The present knowledge suggests that cessation of smoking and treatment of hypertension and diabetes are the principal preventive actions, whereas treatment of hypercholesterolaemia seems less important. Obviously, a patient with intermittent claudication complaints should be treated in accordance with the rule ‘stop smoking and keep walking’ to prevent symptom progression and to improve the level of functioning. Furthermore, improvement of the atherosclerotic risk-factor profile is of significance for prevention of coronary heart disease and cerebrovascular disease in claudicants and asymptomatic PAOD patients: patients with an abnormal non-invasive test result such as an ankle-brachial pressure index lower than 0.90–1.00.[1,42,52]

The ankle-brachial pressure index, measured with a Doppler probe and a sphygmomanometer, is a reproducible and valid diagnostic tool suitable for use in primary care.[42,52] In addition, the height of the ankle-brachial pressure index is inversely associated with disease severity and the occurrence of cardiovascular events.[37,48] Thus, in patients over 50 years of age with one or more conventional atherosclerotic risk factors, assessment of the ankle-brachial pressure index by the GP could provide additional information on the risk of developing manifest atherosclerotic disease.

Key points

- In the general population, only 5–10% of PAOD patients experience symptom progression. This is lower than had been reported in referral-based studies (25%).
- Claudicants, as well as asymptomatic PAOD patients, frequently have co-existing cardiovascular diseases and are at high risk for developing non-fatal and fatal coronary heart disease.
- In subjects aged over 50 years with presence of cardiovascular risk factors, measurement of the ankle-brachial pressure index is appropriate.
- Patients with symptomatic as well as asymptomatic atherosclerosis in the legs, especially men, should be carefully monitored with regard to their cardiovascular risk profile.
- Preventive activities in primary care should focus primarily on smoking cessation and treatment of diabetes and hypertension.

References

1. Vogt MT, Wolfson SK, Kuller LH. Lower extremity arterial disease and the aging process: a review. *J Clin Epidemiol* 1992; **45:** 529-542.
2. Balkau B, Vray M, Eschwege E. Epidemiology of peripheral arterial disease. *J Cardiovasc Pharm* 1994; **23 (Suppl 3):** S8-S16.
3. Fowkes FGR, Housley E, Cawood EHH, *et al*. Edinburgh Artery Study: Prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1991; **20(2):** 384-392.
4. Stoffers HEJH, Rinkens PELM, Kester ADM, *et al*. The prevalence of asymptomatic and unrecognized peripheral arterial occlusive disease. *Int J Epidemiol* 1996; **25:** 282-290.
5. Khaira HS, Hanger R, Shearman CP. Quality of life in patients with intermittent claudication. *Eur J Vasc Endovasc Surg* 1996; **11:** 65-69.
6. European Working Group on critical leg ischaemia. Second European consensus document on chronic critical leg ischaemia. *Circulation* 1991; **84 (Suppl IV):** IV1-IV26.
7. Schadt DC, Hines EA, Juergens JL, Barker NW. Chronic atherosclerotic occlusion of the femoral artery. *JAMA* 1961; **175(11):** 937-940.
8. Hughson WG, Mann JI, Tibbs DJ, *et al*. Intermittent claudication: Factors determining outcome. *BMJ* 1978; **1:** 1377-1379.
9. Naschitz JE, Ambrosio DA, Chang JB. Intermittent claudication: Predictors and outcome. *Angiology* 1988; **39:** 16-22.
10. Cronenwett JL, Warner KG, Zelenock GB, *et al*. Intermittent claudication. *Arch Surg* 1984; **119:** 430-436.
11. Jonason T, Ringqvist I. Factors of prognostic importance for subsequent rest pain in patients with intermittent claudication. *Acta Med Scand* 1985; **218:** 27-33.
12. Dormandy JA, Murray GD. The fate of the claudicant - A prospective study of 1969 claudicants. *Eur J Vasc Surg* 1991; **5:** 131-133.
13. O'Riordan DS, O'Donnell JA. Realistic expectations for the patient with intermittent claudication. *Br J Surg* 1991; **78:** 861-863.
14. Källerö KS. Mortality and morbidity in patients with intermittent claudication as defined by venous occlusion plethysmography. A ten-year follow-up study. *J Chron Dis* 1981; **34:** 455-462.
15. Lassila R, Lepäntalo M, Lindfors O. Peripheral arterial disease. Natural outcome. *Acta Med Scand* 1986; **220:** 295-301.
16. Jelnes R, Gaardsting O, Hougaard Jensen K, *et al*. Fate in intermittent claudication: Outcome and risk factors. *BMJ* 1986; **293:** 1137-1140.
17. Rosenbloom MS, Preston Flanigan D, Schuler JJ, *et al*. Risk factors affecting the natural history of intermittent claudication. *Arch Surg* 1988; **123:** 867-870.
18. Tugwell PX. How to read clinical journals: III. To learn the clinical course and prognosis of disease. *CMA Journal* 1981; **124:** 869-872.
19. Silagy CA. An analysis of review articles published in primary care journals. *Fam Pract* 1993; **10:** 337-341.
20. Davey Smith G, Shipley MJ, Rose G. Intermittent claudication, heart disease risk factors, and mortality. The Whitehall Study. *Circulation* 1990; **82:** 1925-1931.
21. Dagenais GR, Maurice S, Robitaille NM, *et al*. Intermittent claudication in Quebec men from 1974-1986: The Quebec cardiovascular study. *Clin Invest Med* 1991; **14:** 93-100.
22. Reunanen A, Takkunen H, Aromaa A. Prevalence of intermittent claudication and its effect on mortality. *Acta Med Scand* 1982; **211:** 249-256.
23. Agner E. Natural history of angina pectoris, possible myocardial infarction and intermittent claudication during the eighth decade. *Acta Med Scand* 1981; **210:** 271-276.
24. Vogt MT, Cauley JA, Newman AB, *et al*. Decreased ankle/arm blood pressure index and mortality in elderly women. *JAMA* 1993; **270:** 465-469.
25. Kornitzer M, Dramaix M, Sobolski J, *et al*. Ankle/arm pressure index in asymptomatic middle-aged males: an independent predictor of ten-year coronary heart disease mortality. *Angiology* 1995; **46:** 211-219.
26. Widmer LK, Greensher A, Kannel WB. Occlusion of peripheral arteries. A study of 6,400 working subjects. *Circulation* 1964; **30:** 836-842.
27. Ögren M, Hedblad B, Isacsson S-O, *et al*. Non-invasively detected carotid stenosis and ischaemic heart disease in men with leg arteriosclerosis. *The Lancet* 1993; **342:** 1138-1141.
28. Ögren M, Hedblad B, Jungqist G, *et al*. Low ankle-brachial pressure index in 68-year-old men: prevalence, risk factors and prognosis. *Eur J Vasc Surg* 1993; **7:** 500-506.
29. Hedblad B, Ögren M, Janzon L, *et al*. Low pulse-wave amplitude during reactive leg hyperaemia: an independent, early marker for ischaemic heart disease and death results from the 21-year follow-up of the prospective cohort study "men born in 1914", Malmö, Sweden. *J Int Med* 1994; **236:** 161-168.
30. Kannel WB, Skinner JJ, Schwartz MJ, Shurtleff D. Intermittent claudication. Incidence in the Framingham Study. *Circulation* 1970; **61:** 875-883.
31. Newton Peabody C, Kannel WB, McNamara PM. Intermittent claudication. Surgical significance. *Arch Surg* 1974; **109:** 693-697.
32. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: The Framingham Study. *J Am Geriatr Soc* 1985; **33:** 13-18.
33. Stokes J, Kannel WB, Wolf PA, *et al*. The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years of follow-up in the Framingham study. *Circulation* 1987; **75 (Suppl V):** V65-V73.
34. Criqui MH, Coughlin SS, Fronek A. Non-invasively diagnosed peripheral arterial disease as a predictor of mortality: Results from a prospective study. *Circulation* 1985; **72(4):** 768-773.
35. Criqui MH, Langer RD, Fronek A, Feigelson HS. Coronary disease and stroke in patients with large-vessel peripheral arterial disease. *Drugs* 1991; **42 (Suppl 5):** 16-21.
36. Criqui MH, Langer RD, Fronek A, *et al*. Mortality over a period of 10 years in patients with peripheral arterial disease. *New Engl J Med* 1992; **326:** 381-386.
37. Leng GC, Fowkes FGR, Lee AJ, *et al*. Use of ankle-brachial pressure index to predict cardiovascular events and death: a cohort study. *BMJ* 1996; **313:** 1440-1444.
38. Leng GC, Lee AJ, Fowkes FGR, *et al*. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1996; **25:** 1172-1181.
39. Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull WHO* 1962; **27:** 645-658.
40. Rose G, McCartney P, Reid D. Self-administration of a questionnaire on chest pain and intermittent claudication. *Br J Prevent Soc Med* 1977; **31:** 42-48.
41. Fowkes FGR. The measurement of atherosclerotic peripheral arterial disease in epidemiological surveys. *Int J Epidemiol* 1988; **2:** 248-254.
42. Stoffers HEJH, Kester ADM, Kaiser V, *et al*. The diagnostic value of the measurement of the ankle-brachial systolic pressure index in primary health care. *J Clin Epidemiol* 1996; **49:** 1401-1405.
43. Stoffers HEJH, Kester ADM, Kaiser V, *et al*. Diagnostic value of signs and symptoms associated with peripheral arterial occlusive disease seen in general practice: A multivariable approach. *Med Dec Making* 1997; **17:** 61-70.
44. Stoffers HEJH, Kaiser V, Kester ADM, *et al*. Peripheral arterial occlusive disease in general practice: the reproducibility of the ankle-arm systolic pressure ratio. *Scand J Prim Health Care* 1991; **9:** 109-114.
45. Dormandy J, Mahir M, Ascady G, *et al*. Fate of the patient with chronic leg ischaemia. *J Cardiovasc Surg* 1989; **30:** 50-57.
46. McGrae McDermott M, McCarthy W. Intermittent Claudication. The natural history. *Surgical Clinics of North America* 1995; **75:** 581-591.
47. McDaniel MD, Cronenwett JL. Basic data related to the natural history of intermittent claudication. *Ann Vasc Surg* 1989; **3:** 273-277.
48. McGrae McDermott M, Feinglass J, *et al*. The ankle-brachial index as a predictor of survival in patients with peripheral vascular disease. *J Gen Intern Med* 1994; **9:** 445-449.

49. Vogt MT, McKenna M, Wolfson SK, Kuller LH. The relationship between ankle brachial index, other atherosclerotic disease, diabetes, smoking and mortality in older men and women. *Atherosclerosis* 1993; **101:** 1991-1202.
50. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis* 1991; **87:** 119-128.
51. Van Ree J. Who is at risk of intervention? The role of the general practitioner in preventive cardiology. *Eur J Gen Pract* 1995; **1:** 99-100.
52. Hiatt WR, Marshall JA, Baxter J, *et al*. Diagnositic methods for peripheral arterial disease in the San Luis valley diabetes study. *J Clin Epidemiol* 1990; **43:** 597-606.
53. Kitslaar PJEHM. Consensus diagnostiek en behandeling van arteriële claudicatio intermittens. (Consensus on the diagnosis and treatment of intermittent claudication.) *Ned Tijdschr Geneeskd* 1997; **141:** 2396-2400.

Acknowledgements

This work and the ongoing prospective cohort study (Limburg PAOD Study, part three) is supported by a research grant from the Netherlands Heart Foundation (92.170).

Address for correspondence

JD Hooi, Department of General Practice, Maastricht University, PO Box 616, 6200 MD Maastricht, The Netherlands. E-mail: Jurenne.Hooi @HAG.UniMaas.NL