Peripheral arterial disease : screening, diagnosis, and conservative treatment

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PERIPHERAL ARTERIAL DISEASE

Screening, diagnosis, and conservative treatment

by

Bianca Bendermacher

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Bianca Leonie Walthera Bendermacher

PERIPHERAL ARTERIAL DISEASE

Screening, diagnosis, and conservative treatment

Bianca Bendermacher

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Introduction and outline of the thesis

Atherosclerosis refers to a thickening and hardening of the arteries and loss of blood vessel elasticity. It is a systemic disease that is most frequently associated with fatal and non-fatal myocardial infarction, stroke, and disease of the aorta and lower extremities. Peripheral arterial disease (PAD), that is atherosclerosis of the lower extremities, is an important marker for generalised atherosclerosis and is closely associated with cardio- and cerebrovascular disease.¹ Indeed, the risk of cardiovascular disease (e.g. myocardial infarction, angina pectoris) is two to three fold higher in patients with PAD compared to people without PAD. Hence, an early diagnosis of PAD can for this reason be considerably essential, despite a relatively benign local evolution that characterises natural history of PAD. The most predominant risk factors for atherosclerosis are smoking, hypertension, diabetes mellitus, hypercholesterolemia, and an increasing age. The estimated overall prevalence of PAD among people of 55 years or older varies between 9% and 23%.²

In the 1950s, atherosclerosis was considered an inevitable, irreversible, and degenerative consequence of aging. Today we understand that atherosclerotic plaque progression may be stabilized, and that prevention through risk factor modification can yield significant clinical benefits.

Ankle brachial index

The primary method used to objectively diagnose PAD is the ankle brachial index (ABI), which is the ratio of systolic pressures in the ankles and arms, measured by Doppler ultrasound. In healthy individuals the ABI ratio is greater than 1.00 due to the fact that pulse wave reflection causes the ankle pressure to be 10 to 15 mmHg higher than the brachial arterial systolic pressure. In subjects with PAD, the ABI is below 0.9, indicating a stenosis in one of the arteries in the leg. The ABI is a simple, inexpensive diagnostic test for PAD and is the clinical golden standard in general practice.

Lower extremity pressure measurements were first described in 1933³ and Travis Winsor was first to report that the ankle pressure is usually decreased if the arteries in the lower limb are obstructed.⁴ In the sixties, Strandness and Bell described the use of pressure measurements in the lower extremities with a mercury strain gauge as a useful technique for the study of PAD.⁵ An inflatable cuff was placed over the lower leg to constrict the ankle arteries. This cuff was connected to a glass manometer filled with mercury to measure the pressure exerted onto the ankle. Shortly after this description, Strandness began to apply the Doppler ultrasound to measure the ankle pressures, which was first adapted to study velocity patterns in arteries in 1959.⁶

The term "pressure drop" was used to observe PAD, defined as the brachial artery systolic pressure minus digital artery systolic pressure.⁷ Later, the ankle pressure measurement or ABI was considered as an adequate screening measurement for the presence of PAD and a reliable indicator for the magnitude of the problem. In 1970, Yao was the first to report that the severity of disease correlated to the drop in ABI.⁸

The Doppler effect refers to the Austrian physicist Christian Johann Doppler, who made an important discovery regarding the relative motion of both light and sound waves. In 1842 he presented his mathematical formula which relates the frequency of a source to its velocity relative to an observer. Although this effect is named after Doppler, it was actually the Dutch scientist and meteorologist Buys Ballot who first tested Doppler's hypothesis in practice three years after Doppler developed his mathematical formula. Ballot tested the hypothesis on the railway between Utrecht and Amsterdam, using a locomotive capable of attaining the speed of 40 mph, to pull an open cart in which horn players were riding. Ballot observed changes in the apparent pitch of the notes played by the musicians as they approached or receded. Similarly, ultrasound waves scattered by moving blood exhibit the same effect, and reveal the speed with which blood is moving. Since the sixties, Doppler sonography has been chiefly used in angiology. The first results about the use of an ultrasonic flow detector to evaluate PAD were reported in 1968 by Yao et al.⁹ He also first presented the findings that by the use of transcutaneous Doppler flow in conjunction with pressure measurements at the ankle, valuable information could be obtained about the distal arterial bed. Comparison of systolic pressures with angiographic and clinical findings in a large series of cases showed that measurement of the systolic pressures provides a valuable and objective method for the evaluation of patients with arterial occlusive disease of the extremities.¹⁰

To honour the Dutch scientist, founder of the blood pressure measurement by ultrasonic flow changes, it would be respectable to indicate the blood pressure with BB instead of RR, which refers to the Italian medical doctor Scipione Riva-Rocci, who developed the mercury sphygmomanometer.

Nowadays, the ankle pressures are always measured by Doppler ultrasound. More recently, the ABI has been developed as an epidemiological tool for defining the natural history of PAD.¹¹ The use of the ABI in general practice, both as a diagnostic tool as a well as a screening tool will be illustrated in this thesis.

Exercise therapy

Treatment of PAD is aimed to reduce its clinical symptoms and to prevent or reduce local tissue loss. Secondary, treatment is aimed to prevent general complications, such as coronary heart disease and cerebrovascular disease. Intermittent claudication is the main symptom of PAD and is defined as leg pain in the calf of one or both legs that occurs by walking, and is relieved only by rest. The primary and most effective treatment for people with intermittent claudication is exercise therapy¹², which was first suggested by Wilhelm Erb, a German Professor in internal medicine, specialised in neurology.¹³ In that period of time, at the end of the 19th century, rest was thought to be the first treatment option, followed by exercise therapy at a low workload as soon as improvement was experienced after the initial period of rest. Erb described the results of one of his patients showing an improvement from being able to walk only several minutes to over 4 hours without complaints.¹³

In 1924, one of the first exercise programs was developed for patients with PAD, consisting of passive movements.¹⁴ It was theorized that blood vessels would accept a greater function in blood transport if they were alternately emptied and distended. However, this was not confirmed by blood flow data on 10 normal subjects and 19 patients.¹⁵ Although passive postural movements caused no change, active exercise in contrast, did increase the flow during and shortly after the exercise.¹⁶ The first studies on training patients with PAD showed that gangrenous lesions at the feet healed faster when patients were put on a walking program¹⁷, with subjective improvements of complaints.¹⁸ Based on clinical impressions, it was theorized that speed of blood flow, and not ischemia, causes an increase in collateral circulation and that exercise is the simplest, most effective method for augmenting the circulation.¹⁹

In the early sixties, it was emphasized that patients should not increase the tempo of walking above 60 steps per minute or reach the stage of claudication pain. Schlüssel reported significant increases in pain free walking distance and maximal walking distance using this training program in 20 patients with intermittent claudication.²⁰ In 1966, the first randomized controlled trial of exercise therapy examined a supervised exercise therapy program versus observation. In this study, it was for the first time the training went beyond the pain free walking distance. No difference in muscle blood flow was found in this study, although the exercise group significantly increased their maximal walking distance and pain free walking distance compared to little change in the control group.²¹

A higher workload has been shown to result in a greater post exercise hyperemia of the muscle.²² Within limits, it seems logical to assume that the greater the ischemia, the greater is the need for adaptation by the blood vessels. This was supported in the coronary arteries, showing a collateral circulation which was proportional to the degree of arterial constriction.²³ Skinner and Strandness described in 1967 that the optimal training load seemed to be 75% of the maximal walking distance. This was based on their study showing that at this workload the pressure gradient, as well as the amount of ischemia, and the amount of post-exercise hyperemia increased, without causing undue fatigue.¹⁶

A more recent meta-analysis describes that the optimal exercise program for the treatment of intermittent claudication in patients with PAD should be based on intermittent walking to near-maximal pain during a program of at least 6 months.²⁴ Most exercise programs prescribed to patients with PAD are based on single oral advice and performed in a home-based setting without supervision. This is probably due to the fact that supervised, clinic-based exercise programs are only available in a few centres worldwide. In this thesis the clinical benefits of supervised exercise therapy programs compared to non-supervised programs in patients with PAD will be studied. Furthermore, the first results of a new community-based concept of supervised exercise therapy, the so called Network for Exercise Therapy, Parkstad (NETP), will be reported.

Outline of the thesis

The first part of this thesis focuses on the use of the ABI in general practice and on the conservative treatment of PAD. For the use of the ABI, the feasibility as a diagnostic tool in symptomatic patients as well as a screening tool in subjects at risk for atherosclerosis was studied. The conservative treatment possibilities will be outlined, mainly determining the optimum form of exercise therapy treatment in daily practice. Vascular interventions will be left out of account in this thesis.

Part one

The PREVALENT study: feasibility of the ankle brachial index

It has been shown that individuals with an ABI below 0.9 were twice as likely to have cardiovascular disease²⁵, and men with an ABI below 0.9 have a fourfold risk of cerebrovascular disease compared to those with normal pressure indexes.²⁶ However, the majority of patients with PAD are asymptomatic or have leg symptoms other than classic intermittent claudication. It is estimated that only 22% of patients with PAD are symptomatic.²⁷ General practitioners can and must play a key role in recognition, diagnosis and treatment of risk factors of patients with PAD. Assessment of ABI in patients with symptoms suggestive of intermittent claudication is an effective diagnostic tool for PAD and is the clinical standard in primary care.²⁸ However, it has been shown that in only 10% of patients referred to a vascular out-patient clinic, an ABI measurement had been performed by the general practitioner.²⁹ A diagnostic questionnaire for PAD that has been used in epidemiological studies could be valuable in daily general practice to avoid the time-consuming measurement of the ABI.

Chapter two describes the diagnostic value of the Edinburgh Claudication Questionnaire compared to the ABI in symptomatic patients. In **Chapter three** the ABI is used as a screening tool in asymptomatic subjects with at least one vascular risk factor. A clinical prediction model was developed which may function as an effective tool for the general practitioner to effectively screen the high risk population in daily practice. **Chapter four** outlines the feasibility of the ABI as a screening tool is expounded in time-investment. In **Chapter five** of this part, the hypothesis that an ABI above 1.4 is mainly caused by the presence of diabetes mellitus is tested and refuted.

Part two

Conservative treatment of PAD

Treatment of PAD is aimed to reduce the clinical symptoms of intermittent claudication, to prevent or reduce local tissue loss, and to prevent general complications, such as coronary heart disease and cerebrovascular disease. **Chapter six** will focus on vascular risk factor modification and antiplatelet therapies for patients with both symptomatic and asymptomatic PAD, as well as on currently available strategies for relief of symptomatic PAD. In **Chapter seven** supervised exercise therapy is compared with non-supervised exercise therapy in patients with intermittent claudication according to several clinical trials using a meta-analysis. In the Netherlands for instance, the current

prescription of exercise therapy consists mainly of a single "go home and walk" advice by the general practitioner, sometimes with an additional brochure. It is reported that exercise therapy is not undertaken by almost half of the patients with intermittent claudication, whereas the most important barrier for performing walking exercise is a lack of supervision. Currently, exercise therapy in a supervised, clinic-based setting is only available in a few centres. Consequently, there is a limited capacity with an increase in transport costs for patients. To lower costs, and to offer patients with PAD the possibility of a supervised exercise therapy program closer to their homes, a new concept of community-based supervised exercise was developed and implemented, resulting in the Network for Exercise Therapy, Parkstad.³⁰ This network consists of 29 physiotherapeutic practices equally dispersed over the southeast part of Limburg and the department of physiotherapy of the Atrium Medical Centre. Patients with PAD, eligible for exercise, are referred to a physiotherapist for supervised exercise therapy for the period of 12 months. In **chapter eight** the differences are outlined between clinic-based and community-based supervised exercise therapy, as well as the development of the Network for Exercise Therapy Parkstad. **Chapter nine** shows the first results of supervised exercise therapy in intermittent claudication provided in a community-based physiotherapeutic setting. The final **Chapter ten** shows the clinical benefits of supervised exercise therapy in patients with recurrent complaints of intermittent claudication after a previous successful vascular intervention in the lower extremities.

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2

Symptomatic peripheral arterial disease: the value of a validated questionnaire and a clinical decision rule

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Abstract

Introduction: If a validated questionnaire, when applied to patients reporting with symptoms of intermittent claudication, could adequately discriminate between those with and without peripheral arterial disease (PAD), general practitioners could avoid the diagnostic measurement of the ankle brachial index (ABI). To investigate the Edinburgh Claudication Questionnaire (ECQ) in general practice and to develop a clinical decision rule based on risk factors to be able to easily assess the likelihood of PAD in this setting.

Methods: This observational study included patients of ≥ 55 years visiting the general practitioner for symptoms suggestive of intermittent claudication or with one risk factor. The ECQ and the ABI were performed. The prevalence of PAD, defined as $ABI < 0.9$, was related to risk factors using logistic regression analyses on which a clinical decision rule was developed and related to the presence of PAD.

Results: Of the 4,790 included patients visiting the general practitioner with symptoms suggestive of intermittent claudication, 4,527 were eligible for analyses. The prevalence of PAD in this group was 48.3%. The sensitivity of the ECQ was only 56.2%. The prevalence of peripheral arterial disease in a clinical decision rule that included age, male sex, smoking, hypertension, hypercholesterolemia, and a positive ECQ, increased from 14% in the lowest to 71% in the highest category.

Conclusion: This study indicates that the ECQ alone has an inadequate diagnostic value in detecting patients with PAD. In patients with complaints suggestive of intermittent claudication the ABI should be performed to diagnose PAD, although our clinical decision rule could help to differentiate between extremely high and lower prevalences of PAD.

Background

Atherosclerosis is a systemic disease leading frequently to myocardial infarction, stroke, and disease of the aorta and peripheral arteries. Peripheral arterial disease (PAD), that is atherosclerosis of the lower extremities, though being a chronic condition with a relatively benign prognosis locally, is an important marker for generalised atherosclerosis and is closely associated with cardio- and cerebrovascular disease.¹ The incidence of acute (non-) fatal cardiovascular disease is two to three times higher in patients with arterial disease in the lower extremities compared to people with no atherosclerosis in the peripheral arteries.² It has been shown that individuals with an ankle brachial index (ABI) below 0.9 were twice as likely to have cardiovascular disease³, and men with an ABI below 0.9 have a fourfold risk of cerebrovascular disease compared to those with normal pressure indexes.² However, the majority of patients with PAD are asymptomatic or have leg symptoms other than classic intermittent claudication, the main symptom of PAD. It is estimated that only 22% of patients with PAD are symptomatic.⁴

General practitioners can and must play a key role in recognition, diagnosis and treatment of risk factors of patients with PAD. Assessment of the ABI in patients with symptoms suggestive of intermittent claudication is an effective diagnostic tool for PAD and is the clinical standard in primary care.⁵ However, it has been shown that in only 10% of patients referred to a vascular out-patient clinic a prior ABI measurement had been performed.⁶

The Edinburgh Claudication Questionnaire (ECQ) is a validated questionnaire to diagnose intermittent claudication in epidemiological surveys of PAD⁷. It has an established effectiveness for the use in epidemiological studies of PAD. If this questionnaire, when applied to patients reporting with symptoms of intermittent claudication, could adequately discriminate between those with and without PAD, general practitioners could avoid the diagnostic measurement of the ABI. Furthermore, a clinical decision rule could be useful to differentiate between patients reporting with symptoms having a low or a high likelihood of the presence of PAD.

The aim of this study was threefold: to investigate the clinical applicability of the ECQ in daily general practice, using a large population presenting with symptoms suggestive of intermittent claudication among a representative number of general practices; to develop a clinical decision rule based on generally accepted risk factors for PAD to easily assess the likelihood of PAD; and to evaluate a combination of the final decision rules to assess their diagnostic value.

Patients and methods

Study population

This observational study was conducted from October 2002 to February 2005 among 955 general practices. Patients of ≥ 55 years, visiting with symptoms deemed to be

suggestive of intermittent claudication according to the general practitioner (but without confirmation by ABI) were eligible and were asked for informed consent.

Assessment of risk factors

The following risk factors were assessed by the general practitioner: smoking, diabetes, hypertension, hypercholesterolemia, a family history of vascular disease (<60 years), previous myocardial infarction, history of angina pectoris, angioplasty, coronary bypass surgery, and a prior ischemic stroke. Smoking was recorded as current, former (a history of ≥ 10 pack years), and never smokers. Diabetes was present if the serum fasting glucose level was ≥ 6.0 mmol/l and/or if glucose lowering medication was prescribed. Patients using glucose lowering medication with a fasting glucose level <6.0 mmol/l were considered to be adequately treated. A blood pressure of $\geq 140/90$ mmHg, and/or the use of antihypertensive medication were defined as hypertension. Adequately treated hypertension was defined as a blood pressure $\leq 140/90$ mmHg while using antihypertensive medication. Hypercholesterolemia was defined as a serum total cholesterol of ≥ 5.0 mmol/l and/or the use of cholesterol lowering medication, and was considered as adequately treated when below 5.0 mmol/l. If a first grade relative had experienced a cardiovascular event below 60 years of age, a family history of vascular disease was considered to be present.

Assessment of the Edinburgh Claudication Questionnaire

In all patients the ECQ was completed (Table 1). Patients were not be considered to have intermittent claudication if pain was located in the hamstrings, feet, joints or appeared to radiate, in the absence of any calf pain.

Assessment of the ankle brachial index

First the systolic brachial blood pressure was measured by auscultation or Doppler sound of 8 MHz at both arms, after which the systolic pressures of the dorsalis pedis and posterior tibial arteries were measured at malleolar level by Doppler sound. The ABI was calculated for each leg by dividing the highest systolic ankle pressure by the highest brachial systolic pressure. The practice assistant of the general practitioner was able to perform the ABI measurement. PAD was defined as an ABI less than 0.9 in one or both legs.

Analyses

The primary outcome measurement was PAD. The used cut-off point of the ABI was 0.9. This is used in the majority of recent studies and is reported to have a sensitivity of 95% and a specificity of 99% for angiographically confirmed PAD.⁸ All patients with an ABI between 0.9 and 1.4 in both legs were considered normal. Since a high ABI (>1.4) appears to correlate similarly to a low ABI to mortality⁹, we excluded patients with an ABI above 1.4 in one or both legs and without PAD as defined above from the reference group. This was to prevent underestimation of PAD prevalence.

The characteristics of patients with symptoms suggestive of intermittent claudication

were compared between participants with and without PAD using the Students' T-test for continuous variables and the Chi-square test for binary variables. Statistical analyses were preformed using SPSS 11.0.

The prevalence of PAD was compared to risk factors and ECQ using multivariate logistic regression analyses. The beta coefficients that resulted from the regression analyses were converted into odds ratios (OR). Based on these OR, a clinical decision rule was developed. Finally, the outcomes of this clinical decision rule were compared to the presence of PAD.

Results

The study included 4,790 patients with symptoms deemed suggestive of intermittent claudication by the general practitioner. Of these, 181 (3.8%) patients had to be excluded from the analyses since their ABI was above 1.4 in one or both legs (without an ABI below 0.9 in the other leg). In addition, ABI ratio data were missing in 82 (1.7%) patients, leaving 4,527 patients for analyses. The general demographics are shown in Table 2.

The prevalence of PAD in the study group was 48.3%. As shown in Table 2, most of the risk factors were statistically significantly more prevalent in patients with PAD. There was no significant difference in the prevalence of diabetes between the participants with a low and a normal ABI.

Edinburgh Claudication Questionnaire

In 300 (6.6%) patients data were incomplete to assess the ECQ, resulting in an analysis of 4,227 patients. The sensitivity of the ECQ for detecting an ABI below 0.9 was 56.2%, resulting in a positive predictive value of 59.4% and a negative predictive value of 60.7%. The sensitivity of the ECQ appeared to increase with the number of risk factors present. The relationship between the ABI and the ECQ is depicted in Table 3.

Multivariate model

Using the stepwise logistic regression analysis, diabetes (p=0.05), a positive family history (p=0.35), a prior cardio- (p=0.66) or neurovascular event (p=0.30), and the body mass index (p=0.18) were consistently removed from or not included in the final model. The final model showed a significantly increased risk of PAD with increasing age (OR: 1.28 per 5 years; 95% confidence interval (CI): 1.23-1.36; p<0.001), male sex (OR: 1.22; 95% CI: 1.05-1.42; p=0.009), smoking, both former (OR: 1.87; 95% CI:1.56-2.25; p<0.001) and currently smoking (OR: 3.78; 95% CI: 3.17-5.52), the presence of hypertension (OR: 1.67; 95% CI: 1.39-2.00; p<0.001), adequately treated hypertension (OR: 1.35; 95% CI: 1.20-1.61; p=0.001), the presence of hypercholesterolemia (OR: 1.33; 95% CI: 1.15-1.54; p<0.001), and a positive ECQ (OR: 1.92; 95% CI: 1.67-2.22; p<0.001). To translate the OR to an easy clinical decision rule, an OR of 1 was taken as 0 risk factor points, increasing with 1 risk factor point per increase of the OR with approximately 0.33. In Table 4 the clinical decision rule is shown.

Prevalence of peripheral arterial disease in relation to clinical rule

The prevalence of PAD according to the clinical decision rule increases proportionately to increasing score with a prevalence of PAD of 14% in the lowest to 71% in the highest category (Table 5).

Discussion

Summary of main findings

The prevalence of ABI verified PAD in a large cohort of patients with complaints suggestive of intermittent claudication in primary care setting was 48.3%. This non-specificity of complaints for PAD is consistent with findings in previous studies.¹⁰ Since more aggressive prophylactic treatment of risk factors is only advocated in patients with a high risk for cardiovascular diseases, an ABI measurement to confirm the diagnosis of PAD seems necessary.

Among patients with complaints suggestive of intermittent claudication, higher age, male sex, smoking, hypertension and hypercholesterolemia were significantly associated with PAD. However, even in the lowest risk category the prevalence of peripheral arterial disease was still 14% and only 71% in the highest category.

Of the patients with PAD, in 43.8% the diagnosis would have been unjustly rejected if physicians had relied solely on the ECQ. This suggests that the ECQ is of limited value in diagnosing PAD in general practice.¹¹ The ECQ was earlier reported to have a high sensitivity (82.8%) and specificity (100%).⁷ However, this study used patient history taken by a physician as a reference. In our study, where the ABI was used as a reference, the sensitivity appeared to be only 56.2%.

Strengths and limitations of the study

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

While the ability of general practitioners to identify PAD seems good (positive predictive value of 48.3%), we are unable to report on the negative predictive value based on the design of the study.

The presence of hypertension, hypercholesterolemia and diabetes were based on a single measurement or on the established diagnosis of the general practitioner, and not verified according to the criteria of established guidelines.¹²⁻¹⁴ Hence, misclassification could have occurred, resulting in the underestimation of the role of the particular risk factors with respect to the prevalence of PAD.

Furthermore, palpation of the peripheral arteries has a high negative predictive value¹⁵, which could have lead to a more specific population if it had been performed. However, it has been shown that this examination is prone to spurious results even in experienced hands, resulting in many unidentified patients with PAD.^{15,16}

Since the ABI measurement was performed by multiple general practitioners or practice assistants, a larger observer variation could have occurred when compared to a central ABI measurement assessment. However, it is reported that this kind of bias appears to

be low.¹⁷ Moreover, the ABI measurement should have been repeated twice according to the guideline of the Dutch College of general practitioners¹⁸ and in this study, the ABI measurement was only performed once. Both biases would lead to an underestimation of the role of the risk factors in relation to the prevalence of PAD. In addition, the assessment of the ECQ and ABI measurement were not performed by independent observers. This might have introduced a diagnostic suspicion bias.

Since the study attempted to derive a prediction rule for patients with symptoms suggestive of intermittent claudication, one could argue that a true validation study of the developed clinical decision rule on a different population is necessary. However, validation of a clinical decision rule, showing that an ABI measurement is necessary independent of the risk score, seems to be worthless due to the expectation that it would produce even lower prediction scores.

Comparison with existing literature

Using solely the ECQ without measurement of the ABI, risk factor management would not be performed in many patients with PAD, which is associated with a high morbidity and mortality due to other atherosclerotic manifestations like myocardial infarction and stroke.

In our study more men were included, suggesting that men more often report complaints suggestive of intermittent claudication.⁴ Once again this study indicated that smoking is a very important risk factor of PAD. The percentages of current and past smoking are comparable with results reported previously.¹⁹ We showed a significant association between the presence of vascular risk factors and a low ABI, in accordance with most previous investigators.¹⁶ The Framingham Heart Study documented a 2.5 fold increase in the risk of PAD in hypertensive men and a 3.9 fold increase in women with hypertension.²⁰ We were able to show the influence of adequate treatment of hypertension, which gave a 0.4 fold decrease in the risk of PAD and is similar to an earlier report.²¹

Our study confirmed the association of high cholesterol levels with atherosclerosis with an OR of 1.4, which is slightly lower compared to the results of an earlier study which found an OR of 1.7.²² No statistically significant association was shown between a low ABI and the presence of diabetes. It is documented that in about 5% of diabetics, the ABI is over 1.10 despite the presence of PAD.²² The sensitivity and specificity of the ABI in patients with type 2 diabetes are lower (70.6% versus 90% and 88.5% versus 99%, respectively).²³ However, a small study of patients with type 2 diabetes showed little additional benefit of toe pressure measurement.²⁴

Although it is suggested that a high rate of comorbidity in PAD patients is the rule in primary care²⁵, our cohort showed no significant association between the presence of coronary heart disease or stroke and a low ABI using multivariate analyses.

Among patients with PAD, prior evidence of coronary heart disease is more common (27%) than a prior stroke (9.4%). No statistically significant relation is shown between a low ABI and ischemic stroke, which is comparable with our study.²⁶

Implications for future research or clinical practice

This study indicates that the ECQ alone has an inadequate diagnostic value in general practice in patients with symptoms suggestive of intermittent claudication. Based on the high risk of the presence of PAD in even our lowest category (14.5%) it seems that in every patient with complaints suggestive of intermittent claudication the ABI should be performed in order to diagnose PAD. However, our clinical rule could differentiate between patient groups with extremely high and lower prevalences of PAD.

Table 1: Edinburgh Claudication Questionnaire

- 1. Do you get a pain or discomfort in either leg on walking?
- 2. Does this pain ever begin when you are standing still or sitting?
- 3. Does this pain occur if you walk uphill or hurry?
- 4. Does this pain occur if you walk at an ordinary pace on the level
- 5. What happens if you stand still?
- 6. In what part of your leg do you feel the pain?

Table 2: Demographic and clinical characteristics of the total population with complaints suggestive of intermittent claudication

	Total population (n=4527)	ABI < 0.9 (n=2187)	0.9 ≤ ABI ≤ 1.4 (n=2340)	OR for ABI<0.9 (95% CI)	P-value
Age (years) – mean (SD)	68.8 (8.5)	70.1 (8.5)	67.7 (8.3)	1.04 (1.03–1.04)	p<0.001
Men – n (%)	2448 (54.1)	1118 (60.3)	1130 (48.3)	1.63 (1.45–1.83)	p<0.001
BMI – mean (SD)	27.3 (11.6)	26.9 (11.9)	27.8 (11.3)	0.95 (0.94–0.97)	p=0.009
Current smokers – n (%)	1570 (34.7)	938 (42.9)	632 (27.0)	2.05 (1.81–2.33)	p<0.001
Ever smoked – n (%)	1532 (33.8)	743 (34.0)	789 (33.7)	2.25 (1.97–2.57)	p<0.001
Never smoked – n (%)	1319 (29.1)	454 (20.8)	865 (37.0)	0.44 (0.39–0.51)	p<0.001
Hypertension – n (%)	3428 (75.7)	1758 (80.4)	1670 (71.4)	1.82 (1.56–2.12)	p<0.001
Diabetes Mellitus – n (%)	1330 (29.4)	664 (30.4)	666 (28.5)	1.12 (0.99–1.28)	p=0.084
Hypercholesterolemia – n (%)	2147 (47.4)	1081 (49.4)	1066 (45.6)	1.23 (1.08–1.40)	p=0.002
Family history – n (%)	1721 (38.0)	788 (36.0)	933 (39.9)	0.85 (0.75–0.96)	p=0.008
Coronary heart disease – n (%)	1153 (25.5)	591 (27.0)	562 (24.0)	1.17 (1.03–1.34)	p=0.02
Stroke or TIA – n (%)	406 (9.0)	206 (9.4)	200 (8.5)	1.11 (0.91–1.37)	p=0.300
No vascular risk factor present – n (%)	137 (3.0)	28 (1.3)	109 (4.7)	0.27 (0.17–0.40)	p<0.001
Two risk factors present – n (%)	1579 (34.9)	758 (34.7)	821 (35.1)	0.95 (0.84–1.08)	p=0.463
Three or more risk factors present – n (%)	1768 (39.1)	987 (45.1)	781 (33.4)	1.70 (1.50–1.92)	p<0.001

ABI: ankle brachial index; SD: standard deviation; TIA: transient ischemic attack; OR: odds ratio; CI: confidence interval

Table 3: Ankle brachial index related to the Edinburgh Claudication Questionnaire

	ABI < 0.9	0.9 ≤ ABI ≤ 1.4	Total
ECQ positive*	1153	788	1941
ECQ negative	898	1388	2286
Total	2051	2176	4227

*Definite and atypical intermittent claudication; ECQ: Edinburgh Claudication Questionnaire; ABI: ankle brachial index

Table 4: Clinical decision rule according to the logistic regression analyses

Risk factor points	Age	Sex	Smoking behaviour	Hypertension	Hyper-cholesterolemia	ECQ
0	55 – 59 years n=822	Female n=1993	Never smoked n=1319	No hypertension n=928	No hyper-cholesterolemia n=2019	Negative ECQ n=2286
+ 1	60 – 64 years n=722	Male n=2448		Hypertension, adequately treated n=941	Hyper-cholesterolemia n=2147	
+ 2	65 – 69 years n=851			Hypertension, not adequately treated n=2487		
+ 3	70 – 74 years n=880		Ever smoked n=1532			Positive ECQ n=1941
+ 4	75 – 79 years n=716					
+ 5	80 – 84 years n=409					
+ 6	≥ 85 years n=127					
+ 8			Currently smoking n=1570			

ECQ: Edinburgh Claudication Questionnaire

Table 5: Risk profile for peripheral arterial disease in patients with leg symptoms suggestive for intermittent claudication

Risk score	Prevalence – n	ABI < 0.9 – n (%)
0 – 3	228	33 (14.5)
4	179	36 (20.1)
5	262	67 (25.6)
6	392	142 (36.2)
7	436	189 (43.3)
8	406	209 (51.1)
9	450	237 (52.7)
10	437	279 (63.8)
11	351	229 (65.2)
12	252	163 (64.7)
≥ 13	259	184 (71.0)

ABI: ankle brachial index

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3

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

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Abstract

Introduction: Measurement of the ankle brachial index (ABI) can provide important information about the presence of subclinical atherosclerosis. Performing the ABI in the overall population is not feasible, but it can be used in a selected population. A simple prediction rule could be of much use to estimate the risk of an abnormal ABI.

Methods: 7,454 patients of ≥ 55 years presenting with at least one vascular risk factor (smoking, hypertension, diabetes, and hypercholesterolemia) and no complaints of intermittent claudication were included in this observational study. Patients were selected by the general practitioner during visiting hours and from medical records. The prevalence of peripheral arterial disease (PAD), defined as an ABI below 0.9, was related to vascular risk factors using regression analyses on which the PREVALENT clinical prediction model was developed.

Results: The overall prevalence of PAD was 18.4%. Since the treatment of subjects with a history of coronary heart disease and cerebrovascular disease will not be influenced by the finding of asymptomatic PAD, these subjects were not taken into account for the development of the clinical prediction model. Analyses showed a significantly increased risk for PAD with increasing age, smoking, and hypertension. The clinical prediction model giving risk factor points per factor (age: 1 point per 5 years starting at 55 years, ever smoked: 2 points, currently smoking: 7 points, and hypertension: 3 points), showed a proportional increase of the PAD prevalence with each increasing risk profile (range: 7.0%–40.6%).

Conclusion: Based on the PREVALENT clinical prediction model, the general practitioner is able to identify a high risk population in which measurement of an ABI is useful.

Introduction

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

Clearly, in subjects at risk due to the presence of one or more vascular risk factors, the detection of asymptomatic PAD may cause a shift from primary prevention to secondary prevention, resulting in more rigorous treatment targets.² In a recent review it has been suggested that the ABI should not be used as a generic screening test due to its low sensitivity to predict future cardiovascular outcomes.⁵ In contrast it should be applied in a focused manner, selecting individuals for whom the yield of this measurement can be expected to be highest.

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

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

Methods

Study population

This observational study was part of the larger PREVALENT study and was conducted from October 2002 to February 2005 the PREVALENT study among 955 general practices in the Netherlands. Subjects of 55 years of age and older, presenting with

at least one vascular risk factor (e.g. smoking, hypertension, diabetes mellitus, and hypercholesterolemia), and no complaints of intermittent claudication, were asked to participate. Excluded were patients with PAD Fontaine stage III and IV. Patients during visiting hours and patients selected from medical records (based on the presence of vascular risk factors) were included by the general practitioner. Informed consent was obtained from eligible patients.

Assessment of risk factors

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

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

Assessment of the ankle brachial index (ABI)

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

Analyses

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

The demographic and clinical characteristics of the asymptomatic subjects were compared between participants with and without PAD using the Students' T-test for binary variables and the Chi-square test for nominal variables.

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

Results

The study included 7,977 subjects without complaints of intermittent claudication. Of these 7,977 subjects, 458 (5.7%) were measured to have an ABI above the 1.4 in one or both legs with no ABI measurement below 0.9 in the other leg. These 458 subjects were excluded for the analyses. In addition, the ankle pressure of either leg could not be obtained in 65 (0.8%) patients, leaving 7,454 patients available for our analyses (Figure 1). The general demographics and clinical characteristics of this cohort are detailed in Table 1.

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

Multivariate model

Using stepwise logistic regression analysis, gender, diabetes mellitus, hypercholesterolemia, a positive family history, and the body mass index were consistently removed from or not included in the final model. Calculations using the final logistic model showed a significantly increased risk for PAD with increasing age (odds ratio (OR): 1.34 per 5 years; 95% confidence interval (CI): 1.29–1.40), smoking behaviour, including ever smoked (OR: 1.4; 95% CI: 1.2–1.6) and current smoking (OR: 2.9; 95% CI: 2.2–4.0), the presence of hypertension (OR: 1.5; 95% CI: 1.3–1.8), adequately treated hypertension (OR: 1.2; 95% CI: 1.1–1.4), the presence of coronary

heart disease (OR: 1.6; 95% CI: 1.4–1.8), and the presence of cerebrovascular disease (OR: 1.3; 95% CI: 1.1–1.6). Based on the assumption that the treatment of patients with a history of a cardiovascular- or cerebrovascular events will not be influenced by the finding of asymptomatic PAD, the previously mentioned risk factors were not taken into account in the final clinical prediction model. To translate the OR to an easy clinical decision rule, an OR of 1 was taken as 0 risk factor points, increasing with 1 risk factor point per increase of the OR with approximately 0.25. In Table 2 the clinical prediction model is shown.

Prevalence of PAD in relation to the clinical decision rule

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

Discussion

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

We demonstrate that the prevalence of asymptomatic PAD in our study was influenced by age, smoking behaviour, hypertension, and the presence of cardio- and cerebrovascular disease. Interestingly, despite the relatively large sample size, there was no statistically significant association between the presence of diabetes mellitus alone and the presence of asymptomatic PAD. This finding is in contrast with earlier studies, which reported that asymptomatic PAD is more common in diabetic subjects.^{18,19}

We have developed a clinical prediction model that can be used to differentiate between patient groups from a lowest risk of 7.0% to a highest risk of 40.6% for the presence of PAD. Identification of asymptomatic PAD may identify those subjects who are at risk to develop vascular complications and who would otherwise not receive adequate risk factor management therapies. When patients with a score above seven points would be selected for an ABI measurement, four patients have to be tested to identify one asymptomatic patient with PAD. Since this seems to be feasible in clinical practice, it can be recommended to screen this population. Based on the data of the current survey, we identified several risk profiles which may obtain a score of seven points or higher. For example, current smoking as a single risk factor satisfies a score of seven, independent of age, while former smokers will only obtain this level when 65 or older, and with the presence of non-adequately treated hypertension.

Clinical implications

The status of current smoking was determined to have a five times greater effect on the presence of asymptomatic PAD compared to a history of smoking. This is comparable with the results of previous studies showing that smoking cessation significantly reduces the prevalence of symptomatic PAD and cardiovascular complications.^{20,21} Hypertension increased the prediction of the presence of asymptomatic PAD with 50% compared to no hypertension, which is comparable with earlier reports.²² However, adequate treatment reduced the increased risk to only 20% compared to non-hypertensive patients.

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

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

It has been shown that the absolute number of coronary events is greater in the lower risk population than in the high risk groups.²⁸ In a prospective study, primarily asymptomatic men and women with an average age of 66 years and an abnormal ABI value were shown to have a relative risk of 6.3 for all cardiovascular disease mortality, and 3.1 for all-cause mortality.³ These relative risks are similar to relative risks seen in the secondary prevention setting.³ It has been estimated that simple screening of those of 50 years or older could potentially prevent around 60.000 major cardiovascular events in Great Britain in the next five years. About 85.000 new cases of angina and intermittent claudication may also be prevented, hence about 1 in 13 treated individuals would acquire some clinical benefit.²⁸

Screening for asymptomatic coronary heart disease or cerebrovascular disease may not be practical, since there are no simple screening tools available at this time. The implication that PAD is strongly associated with coronary heart and cerebrovascular

disease makes ABI measurement probably the most efficient screening tool for systemic atherosclerosis. ABI measurement is a simple, inexpensive diagnostic test with an excellent reproducibility among trained operators.²⁹ In addition, assistants in general practice have shown to be able to perform ABI measurement correctly.³⁰ This may even lower the costs of screening.

Strengths and weaknesses of the study

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

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

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

In this large multi-observer study the measurement of the ABI was performed by multiple general practitioners or practice assistants. This may lead to an observer bias. However, it is reported that this type of bias in regard to the measurement of the ABI is as low as 0.114.^{31,32}

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

Conclusion

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

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

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

ABI: ankle brachial index; NS: not significant; SD: standard deviation

Table 2: Clinical prediction model according to the logistic regression

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

Table 3: Prevalence of PAD according to the clinical prediction model in asymptomatic subjects

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

ABI: ankle brachial index

Figure 1: Inclusion schedule of analysed population

ABI: ankle brachial index

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Applicability of the ankle brachial index measurement as screening device in general practice for high cardiovascular risk individuals

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Abstract

Introduction: Screening with ankle brachial index (ABI) measurement could be clinically relevant to avoid cardiovascular events in subjects with asymptomatic atherosclerosis. To assess the impact of guidelines regarding the use of ABI as a screening tool, the corresponding number needed to screen, including the required time investment, and the feasibility of ABI performance, was assessed.

Methods: 13,038 subjects of ≥ 55 years presenting with symptoms of intermittent claudication and/or presenting with at least one vascular risk factor were included. Guidelines were systematically searched for indications that ABI measurement should be performed. To assess the number needed to screen, a composition of the general population was made, and the time needed to perform the ABI was assessed. The number needed to screen was translated to the setting of a single general practice.

Results: Guidelines recommend the ABI as an additional measurement in selected populations (e.g. persons of ≥ 50 years, or those who appear to be at risk of cardiovascular disease). Approximately 10% of subjects above 55 years are without any vascular risk factor. The mean time necessary for ABI measurement was 17 minutes. Screening of the overall population of ≥ 50 years results in ≈ 731 subjects per general practice who should be screened, resulting in a time-requirement of approximately 5 weeks of full time work. Using an existing clinical prediction model, 213 patients per general practice should be screened for PAD by ABI measurement, corresponding to ≈ 60 working hours for an initial screening measurement.

Conclusion: Screening the entire population of ≥ 50 years, as advised in clinical guidelines, will in our opinion not be feasible in general practice. A more rationale and efficient approach might be screening of subsets of the population of ≥ 55 years based on a clinical prediction model.

Introduction

Peripheral arterial disease (PAD) is a common disease, with a prevalence that increases with age and with the presence of vascular risk factors. The ankle brachial index (ABI) is a simple, inexpensive diagnostic test for PAD. Among well-trained operators, reproducibility is excellent, and the validity of the test for a stenosis above 50% in the arteries of the leg is high, with a sensitivity and specificity of approximately 90% and 98% respectively.¹ The ABI measurement as a diagnostic tool is therefore a very useful non-invasive tool for identifying symptomatic patients with atherosclerosis in primary care. An ABI below 0.9 is associated with an important increased risk of cardiovascular morbidity and mortality.² It is well known that in symptomatic patients with PAD secondary prevention of a cardiovascular event by risk factor management and antiplatelet therapy is effective.

As subjects with asymptomatic atherosclerosis may well benefit from the same preventive measures that are effective in subjects with symptomatic disease, screening of asymptomatic subjects at risk is likely to be clinically useful. The advice to perform a risk assessment whether to initiate a primary prevention strategy in all asymptomatic subjects is consistent with current international clinical practice guidelines including ATP-III³, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC)-VII⁴, the European Guideline⁵, the American Heart Association (AHA) and American College of Cardiology (ACC) recommendations⁶, and the multidisciplinary guideline of cardiovascular risk factor management of the Dutch Institute for Healthcare Improvement (CBO).⁷ The initial risk assessment is recommended to be performed using a multifactorial statistical model such as the Framingham Risk Score⁶. Although ABI measurement is not included in this initial assessment, it is recommended as additional measurement in selected populations, especially in people aged 50 years and older or those who appear to be at risk, since an abnormal ABI provides incremental prognostic information. The cardiovascular morbidity rate for asymptomatic PAD subjects was estimated at 76.8 per 1000 person-years at risk, compared with 13.⁶ for the non-PAD population.⁸ Furthermore, much higher all-cause and cardiovascular mortality rates were observed in asymptomatic PAD subjects (42.8 and 35.8 per 1000 person-years, respectively) compared with non-PAD subjects (10.9 and 2.4 per 1000 person-years, respectively).⁸

Screening for PAD, and consequently generalised atherosclerosis, in asymptomatic subjects could lead to early prevention of cardiovascular morbidity and mortality. Currently, the emphasis is accentuated on the matter of selection of the highest-risk patients using the Framingham Risk Score to maximize the benefit-cost ratio of primary prevention treatment.⁹ The ABI as additional screening measurement could be useful in refining the risk prediction and therefore improve the benefit-cost ratio.

Primary care providers are best positioned to determine the at-risk population in the general population and to initiate educational, lifestyle, and cardiovascular risk

reduction therapies.¹⁰ However, physicians have not readily adopted the screening of asymptomatic PAD in their general practice", and studies on the feasibility of ABI testing for the assessment of overall cardiovascular risk are lacking.

To assess the practical impact of the guidelines regarding the use of the ABI as a screening tool for diagnosing PAD in asymptomatic subjects, the number needed to screen was explored. The impact of this number needed to screen on the required time investment by general practitioners in the Netherlands was studied to be able to explore the feasibility of the ABI in general practice.

Materials and methods

Contemporary guidelines regarding the advice to perform an initial risk assessment for cardiovascular morbidity in clinical practice, were systematically searched for indications that an ABI measurement should be performed.

To assess the number needed to screen, a composition of the general population was made using the census of the Dutch population, provided by the Central Office of Statistics of the Netherlands, and studies reporting the prevalence of vascular risk factors in open study populations.

Furthermore, the time-investment of the ABI measurement was studied as part of the PREVALENT study. This study was conducted from October 2002 to February 2005 in general practices in the Netherlands. Patients of 55 years and older with symptoms of intermittent claudication according to the general practitioner (without confirmation by ABI) and/or presenting with at least one vascular risk factor, were asked to participate in this observational study. There were no exclusion criteria. Informed consent was obtained from eligible patients.

For the measurement of ABI, first the systolic brachial blood pressure was performed by auscultation at both arms, after which the systolic pressures of the dorsalis pedis and posterior tibial arteries were measured at malleolar level by an 8 MHz Doppler sound in both legs. The ABI was calculated for each leg by dividing the highest systolic ankle pressure by the highest brachial systolic pressure. The ABI was measured by the general practitioner or practice assistant. PAD was defined as a single ABI measurement of less than 0.9 in one or both legs.

After completing the case record form, the time required for an ABI measurement was reported for each patient. Furthermore, the general practitioner was asked if he had previous experience with performing the ABI measurement before participating in this study and who actually performed the ABI (e.g. general practitioner or practice assistant).

Finally, to explore the impact of the number needed to screen on the required time investment by general practitioners in the Netherlands, the number needed to screen was translated to general practice and related to the time requirement of an ABI measurement.

Results

Contemporary guidelines

The recent ACC/AHA guideline for the management of patients with PAD recommends that individuals with asymptomatic lower extremity PAD should be identified by measurement of the ABI, so that therapeutic interventions, known to diminish their increased risk of myocardial infarction, stroke, and death, can or may be offered.¹⁰ However, ABI measurement is only recommended as additional measurement in a selected population, e.g. subjects aged 50 years and older or those who appear to be at risk due to the presence of vascular risk factors.

A recent review about the risk of mortality and cardiovascular disease supports the recommendation of the AHA prevention conference that consideration of ABI for risk assessment should be restricted to persons of 50 years and older, or those who appear to be at intermediate or higher risk of cardiovascular disease, such as smokers or diabetics.^{11,12}

Furthermore, the American Diabetes Association (ADA) 2003 Consensus Statement recommends screening for PAD, using ABI, for patients with diabetes older than 50 years, for diabetic patients younger than 50 years of age who have other risk factors for PAD (e.g. smoking, hypertension, hyperlipidemia, or duration of diabetes for more than 10 years).¹³ The rationale for screening subjects with diabetes is that PAD is prevalent in patients with diabetes mellitus and is more commonly asymptomatic and more likely to lead to limb loss if a clinician waits until the onset of symptoms to identify disease.¹¹ It is suggested that the ABI has the potential to increase the sensitivity, specificity, and positive predictive values of cardiovascular risk tables.¹² Although establishment of PAD diagnosis in individuals at-risk has the potential to alter the intensity of treatment goals¹⁰, it should be noted that the impact of early PAD detection on either limb or cardiovascular ischemic event outcomes or on survival, has not yet been evaluated in prospective trials.¹⁰

Population composition in general practice

The overall population of 55 years of age and older in the Netherlands consists of approximately 3.8 million people (23.7%), with approximately 1.7 million male subjects.¹⁴

Smoking

It is reported that in 2004 29% of the people between 50 to 64 years of age currently smoked and 45% had smoked in the past. In the group of 65 years and older, 14% were current smokers and 54% were former smokers.¹⁵ For the Dutch population, this corresponds to an overall percentage of approximately 22.5% current smokers and 48.9% former smokers in the population of 50 years and older. In the population of 55 years and older, these percentages will be slightly less, due to the decreasing prevalence in older subjects.

Hypertension

Due to the recent change in the cut off points for the definition of hypertension, there are no exact data available about the prevalence of hypertension, defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg.¹⁶ The ERGO study showed a prevalence of 27% in the subjects of 55 to 59 years of age.¹⁷ A cross sectional survey consisting of 530 subjects of 55 years and older, found a prevalence of hypertension of 41.7%, defined as systolic blood pressure ≥ 140 mmHg and/or diastolic ≥ 90 mmHg.¹⁸ Based on this, we estimated that there are currently approximately 1.58 million people with hypertension in the Netherlands.

Diabetes mellitus

Overall, there are approximately 474,300 patients with known diabetes mellitus in the Netherlands.¹⁹ Approximately 86% is above 50 years of age, corresponding with approximately 407,900 subjects with diabetes (8.2%).¹⁹ The incidence of new diabetes is estimated to be approximately 58,090 subjects per year, with 82% older than 50 years of age.¹⁹

Hypercholesterolemia

No exact data about the prevalence of hypercholesterolemia are available due to the recent change in the cut off levels for the definition of hypercholesterolemia. Dutch data, using a definition of hypercholesterolemia of 6.5 mmol/l or higher and/or the use of lipid lowering medication, estimated the prevalence of hypercholesterolemia to be 33.9% in the population of 50 to 60 years of age.²⁰

Based on the independent prevalence's of these common vascular risk factors, under the assumption that these are unrelated, it can be calculated that approximately 10% of subjects above 55 years are without any vascular risk factor (22.5% smokers, 27% subjects with hypertension, 8.2% subjects with diabetes mellitus, and 33.9% subjects with hypercholesterolemia). This low percentage is largely explained by current and former smoking behaviour.

Time-investment using the ABI: results of the PREVALENT study

The PREVALENT study included 13,038 patients, performed by 955 general practices. Of the 513 general practitioners who included ≥ 20 patients, 101 (19.7%) recorded to have experience performing the ABI prior to participation in this study. The mean time necessary for ABI measurement in the overall population was 17 minutes (SD: 7.4). In 2,534 subjects (19.4%) ABI was measured by an experienced general practitioner or practice assistant. The influence of experience on the duration of ABI measurement is shown in Table 1.

Feasibility of the ABI as screening tool in general practice

Supposing that a general practice consists of approximately 2,350 patients, screening of the overall population of 50 years and older, according to the guidelines,

corresponds with approximately 31.1% of the total population. This results in a total of approximately 731 subjects per general practice who should be screened by ABI measurement.

Thus, a single screening of ABI in the overall population of 50 years and older would take an investment of approximately 5 weeks (207 hours) of full time work. Hence, a strategy of an ABI measurement in all subjects of 50 years and older to be performed every 5 years carries the burden of one week full time work per year (Figure 1).

Limitation of screening subjects of 50 years and older with at least one vascular risk factor only would not substantially reduce this workload due to the high prevalence of these vascular risk factors.

Discussion

Following the recommendations of the current international guidelines regarding the use of an ABI measurement, will substantially increase the workload of general practitioners. The time requirement of 17 minutes per measurement is comparable with earlier results.²¹ Although in the Netherlands the cost of measurement of the ABI in office practice is reimbursed by healthcare payers by an amount of 51 Euro for each ABI measurement, it is doubtful if the recommendations are feasible and can be followed in general practice.

To our knowledge, no guideline provides information on the necessity of repeating the ABI measurement, let alone its timing in subjects with a normal ABI (≥ 0.9) at first screening. Only for patients with diabetes a recommendation is given to repeat the ABI measurement every 5 years if the initial test is normal.²² One could imagine that in subjects between 50 and 60 years of age with a normal initial ABI, the ABI can decrease over time due to the relatively slow progression of the atherosclerotic process without causing complaints. It is a possibility that subjects with this decrease in ABI should be a prime target for aggressive risk factor management. Hence, it might be preferable to repeat the ABI measurement for screening of the presence of PAD, and consequently generalized atherosclerosis, in subjects with a normal initial ABI.

An alternative strategy could be to focus on restricting an ABI measurement to patients who are at a high risk. For this purpose the PREVALENT clinical prediction model may be used (Table 2 and 3).²³ Taking a score limit of 7 or more risk factor points, resulting in a likelihood of approximately 20% or higher for an ABI below 0.9, the following populations should be screened. First, all current smokers of 55 years or older should be screened by ABI. With a prevalence of current smoking of approximately 22.5% in the population of 50 years and older, approximately 125 patients need to be screened in a general practice. A second population that should be screened for asymptomatic PAD are the subjects of 75 years or older with non-adequately treated hypertension, defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Assuming that in a general practice there are approximately 143 patients of 75 years and older, with approximately 29.6% inadequately treated hypertension, there are

approximately 42 subjects to screen in this subgroup. The final population at risk are subjects of ≥ 65 years with inadequately treated hypertension, and a history of smoking behaviour. Since there are approximately 320 patients of ≥ 65 years, with approximately 29.6% inadequately treated hypertension, and approximately 48.9% former smokers, this results in approximately 46 subjects to screen for asymptomatic PAD in this subgroup. Figure 1 shows the feasibility of the ABI using the clinical prediction model.

Overall, using the PREVALENT clinical prediction model, 213 patients per general practice should be screened for PAD by ABI measurement, corresponding to approximately 60 working hours for an initial screening measurement. Of the screened subjects, 60% to 80% will have a normal ABI (0.9 or higher). Screening these non-PAD subjects every five years, implies that in the following years approximately 130 to 170 subjects a repeated ABI measurement will have to be performed to diagnose asymptomatic PAD, excluding new subjects of 55 years of age. Hence, a strategy of an ABI measurement in these subjects to be performed every 5 years will only take approximately 12 working hours of full time work per year to diagnose asymptomatic PAD (Figure 1).

Based on the PREVALENT clinical prediction model, 60% of the subjects of 55 years and older will not be screened. Of these, approximately 10% will have an ABI below 0.9. However, of the screened population, the diagnosis PAD will be established by ABI measurement in 25%. Overall, approximately 63% of the asymptomatic patients with PAD will be found as a result of screening using clinical prediction model and ABI measurement.

Clinical consequences of detecting a low ABI in asymptomatic subjects

Current U.S. national hypertension and lipid treatment guidelines include all patients with lower extremity PAD, regardless of symptom status, as a high-risk category.¹⁰ In these guidelines, all patients should achieve risk reduction and specific treatment targets comparable to individuals with established coronary artery disease.^{4,24}

Conclusion

Screening for PAD by using ABI in the initial risk assessment is recommended as additional measurement in the population of 50 years and older. Screening the entire population of 50 years and older, will in our opinion not be feasible in general practice, since the work involved is substantial. A more rationale approach might be the screening of subgroups of the population of 55 years and older based on a clinical prediction model. Our calculations suggest that using the PREVALENT clinical risk score, the work load of screening can be reduced by 60% while the majority of asymptomatic patients with PAD (63%) will be detected. Ideally, cost effectiveness of screening with ABI measurement should be assessed in future studies.

Table 1: Influence of experience on measurement time of the ABI

Included patients	Time ABI measurement (minutes)			
	Mean (SD)			
	Experienced		Non-experienced	
	GP	PA	GP	PA
Patient 1	13.5 (5.9) (n=47)	19.7 (9.5) (n=78)	18.0 (8.1) (n=73)	19.1 (8.1) (n=206)
Patient 2	14.2 (5.9) (n=47)	18.8 (8.7) (n=76)	16.7 (6.9) (n=71)	19.0 (7.3) (n=201)
Patient 3	13.1 (5.4) (n=43)	19.6 (10.4) (n=78)	17.1 (7.5) (n=71)	18.8 (7.3) (n=205)
Patient 4	12.4 (4.7) (n=45)	18.4 (7.8) (n=77)	16.6 (7.5) (n=70)	18.1 (7.1) (n=205)
Patient 5	12.6 (5.8) (n=47)	18.4 (6.9) (n=76)	16.4 (9.6) (n=71)	18.1 (6.9) (n=202)
Patient 6 – 10	12.8 (5.7) (n=228)	17.8 (7.4) (n=367)	16.0 (7.8) (n=354)	18.0 (7.5) (n=993)
Patient 11 – 15	12.2 (5.2) (n=211)	17.7 (7.3) (n=355)	15.3 (7.5) (n=341)	17.5 (7.2) (n=947)
Patient ≥ 16	12.5 (5.4) (n=200)	18.0 (7.5) (n=347)	15.5 (7.2) (n=335)	17.4 (6.9) (n=936)

ABI: ankle brachial index; SD: standard deviation; GP: general practitioner; PA: practice assistant

Figure 1: Feasibility of ABI screening

Table 2: Clinical prediction model

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

Table 3: Prevalence of PAD according to the clinical prediction model in asymptomatic subjects

Risk score	Prevalence (n)	ABI < 0.9 (n – %)
0 – 3	1202	84 (7.0)
4	706	84 (11.9)
5	924	134 (14.5)
6	865	151 (17.5)
7	20	178 (19.3)
8	722	170(23.5)
9	448	116 (25.9)
10	470	114 (24.3)
11	331	83 (25.1)
12	241	75 (31.1)
≥ 13	271	110 (40.6)

ABI: ankle brachial index

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Myth busted: The myth of the high ankle brachial index caused by diabetes mellitus

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Abstract

Introduction: The ankle brachial index (ABI) measurement is the standard method in primary care for diagnosing peripheral arterial disease. It is commonly assumed that a high ABI is related to the presence of diabetes, since stiffening of blood vessels and medial arterial calcification is common in these patients.

The aim of this study was to analyse the prevalence of a high ABI in relation to risk factors for atherosclerosis in a community dwelling population.

Methods: 13,038 patients of ≥ 55 years presenting with at least one risk factor and/or with complaints of intermittent claudication were included. The prevalence of a high ABI, defined as above 1.4, was related to vascular risk factors, using logistic regression analyses.

Results: Of the 13,038 patients included, 12,886 were eligible for analyses. The prevalence of an ABI above 1.4 was 5.2%. Although the presence of diabetes when treated inadequately was significantly related to a high ABI (OR=1.28) using univariate analysis, this was lost using multivariate analyses ($p=0.865$). Whereas first-order interaction effects showed no effect on a high ABI, three second-order interactions showed significant effects of the presence of diabetes on a high ABI in the subgroups: elderly women and middle-aged men, men with a high diastolic blood pressure, and men with a history of cerebrovascular disease.

Conclusion: Effects of diabetes on the measurement of a high ABI appeared to be present only in subgroups. Since no direct relation between diabetes and a high ABI was observed, the assumption that a high ABI is often caused by diabetes alone is not supported.

Introduction

The ankle brachial index (ABI) measurement is the standard method in the primary care to diagnose for the presence of peripheral arterial disease (PAD) and an effective screening tool. It is a simple non-invasive test that correlates well with angiographic disease severity and functional symptoms.¹⁻³ The reproducibility of the ABI measurement is considered acceptable with a 95% prediction interval around the measured value of 0.14–0.20.⁴⁻⁶ For an angiographically defined stenosis of 50% or more in a major artery in the leg, the sensitivity of the ABI is approximately 90%, with a specificity between 95–99%.⁷⁻⁹ In patients without PAD, the ABI is greater than 1.0, whereas in PAD, the index is 0.9 or less. An ABI below 0.9 is associated with a high risk of ischemic progression of the limb and a higher possibility for cardiovascular morbidity and mortality.^{12,13}

It is generally believed that a high ABI (>1.4) is related to diabetes mellitus, since generalized stiffening of blood vessels¹⁴, as well as medial arterial calcification¹⁵ are common in diabetic patients. Due to these mechanisms, underlying arteries become incompressible. Indeed, several publications reported that there is a relationship between a high ABI and the presence of diabetes mellitus.¹⁶⁻¹⁸ However, to our knowledge, no study has systematically addressed the possible relationship between a high ABI and the presence of diabetes mellitus.

The aim of this study was to assess the prevalence of a high ABI related to generally accepted risk factors for atherosclerosis, including diabetes mellitus.

Patients and methods

Study population

The PREVALENT study was conducted from October 2002 to February 2005 in 955 general practices in the Netherlands. Patients of 55 years and older with symptoms of intermittent claudication according to the general practitioner (without confirmation by ABI) and/or presenting with at least one vascular risk factor were asked to participate in this observational study. Patients seen during visiting hours and patients selected from medical records (based on the presence of vascular risk factors) were included by the general practitioner. There were no exclusion criteria. Informed consent was obtained from eligible patients. The study protocol was approved by the medical ethics committee of the Atrium Medical Centre Parkstad, the Netherlands.

Assessment of risk factors

The recorded risk factors were age, smoking, diabetes mellitus, hypertension, hypercholesterolemia, body mass index (BMI), complaints suggestive of intermittent claudication, a family history of vascular disease, a previous myocardial infarction, angina pectoris, prior angioplasty or coronary by-pass surgery, and prior ischemic stroke. These data were extracted from the patient file or assessed by the general practitioner during the patient's visit.

Subjects of 55 to 67 years old were defined as middle aged, whereas subjects older than 67 years of age as elderly. Smoking was classified as: never smoked, current smoker, and former smoker with a smoking history of at least 10 pack years. Diabetes was considered to be present if the serum fasting glucose level was higher than 6.0 mmol/l¹⁹ and/or if glucose lowering medication was prescribed. Adequately treated diabetes mellitus was defined as using blood glucose lowering medication and a serum fasting glucose level below 6.0 mmol/l and inadequately treated as a serum fasting glucose level above 6.0 mmol/l despite the use of blood glucose lowering medication. Hypertension was defined as a systolic blood pressure of 140 mmHg or higher, and/or a diastolic blood pressure of 90 mmHg or higher²⁰⁻²², and/or the use of medication for hypertension. Subjects using medication for hypertension with a systolic blood pressure below 140 mmHg and a diastolic blood pressure below 90 mmHg were considered to be adequately treated for hypertension. Hypercholesterolemia was defined as a fasting serum total cholesterol of ≥ 5.0 mmol/l and/or the use of cholesterol lowering medication, whereas sufficiently treated high cholesterol was defined as patients receiving medication with a total cholesterol level below 5.0 mmol/l. A family history of vascular disease was present when at least one first grade relative experienced a vascular event before the age of 60 years.

Assessment of the ankle brachial index

First the systolic brachial blood pressure was measured by auscultation or Doppler ultrasound of 8 MHz at both arms, after which the systolic pressures of both the dorsalis pedis artery and posterior tibial artery were measured at malleolar level by Doppler probe on both legs. The ABI was calculated for each leg by dividing the highest systolic pressure in the ankle by the highest brachial systolic pressure.²³ The ABI was measured by the general practitioner or his/her practice assistant. The cut off point used for a high ABI was >1.4 .

Statistics

The primary outcome measure was a high ABI, defined as an ABI above 1.4 in one or both legs. The prevalence of having a high ABI was assumed to be related to fifteen factors. The main of data-analytic interest was the relationship of the presence of diabetes with a high ABI. Diabetes mellitus, if present, was categorized as adequately treated and inadequately treated and both were contrasted with no diabetes at all. At first, univariate logistic regression analyses was performed for each separate variable. Next, a multivariate logistic regression search procedure was performed with all relevant factors except diabetes, which was deliberately kept within the model to test its net odds ratio (OR) effect on the presence of a high ABI. The result of this phase was a logistic regression model containing diabetes plus all variables having statistically significant effects on the presence of a high ABI: the 'direct-effects' model. Next, all 14 first-order interactions (involving diabetes) were hierarchically introduced into the model to test the statistical significance of their effects on the presence of a high ABI. Finally, all 91 second-order interactions were also hierarchically tested for statistical

significance. If first and/or second order interactions, containing diabetes, were statistically significant, subgroup logistic regression analyses were performed within the classes of the (combination of) other predictive factor(s) involved in the interaction, to gauge the direction and statistical significance of the relationship of diabetes mellitus. Data analysis was performed using SPSS-pc version 12.0. A p-value of less than 0.05 was considered to be statistically significant during the search for the best fitting model.

Results

Univariate analyses

The PREVALENT study included 13,038 subjects. The ankle pressure of one or both legs could not be obtained in 152 (1.2%) subjects, leaving 12,886 subjects available for analysis. The overall prevalence of a high ABI (>1.4) in this population was 5.2% ($n=664$). The univariate relationships of relevant demographic and clinical characteristics and high ABI are presented in Table 1.

Presence or absence of diabetes was not registered in 2.8% of all cases. Of the 5,259 cases with diabetes, only 720 (13.7%) were adequately treated according to the definition used in this study. Contrasting no diabetes with adequately treated diabetes was not statistically significant ($OR=1.14$, 95% CI: 0.81–1.61). The comparison of no diabetes with inadequately treated diabetes showed statistical significance with an OR of 1.28 (95% CI: 1.09–1.51). As presented in Table 1 that the statistically significant risk factors for the presence of a high ABI were BMI ($OR=1.05$), male gender ($OR=1.63$), and inadequately treated diabetes mellitus. The most important statistically significant protective factors for a high ABI were current smoking ($OR=0.51$), both inadequately ($OR=0.51$) and adequately ($OR=0.77$) treated hypertension, complaints suggestive of intermittent claudication ($OR=0.667$).

Multivariate analyses

All predictive factors were entered simultaneously into a multiple logistic regression model. Results of the 'direct-effects' model now showed that diabetes mellitus, both adequately ($OR=1.01$ (95%CI: 0.69–1.48)) and inadequately treated ($OR=1.04$ (95% CI: 0.85–1.28)), has no significant relationship with an ABI above 1.4 ($p=0.87$). This model also contains three statistically significant protective factors, e.g. former smoking ($OR=0.71$), current smoking ($OR=0.43$), complaints of intermittent claudication ($OR=0.71$), and systolic blood pressure ($OR=0.98$), and one statistically significant risk factor, e.g. BMI ($OR=1.07$). Men were statistically significantly at risk for a high ABI compared to women ($OR=2.29$). Age was added to the model irrespective of the significance of its effect in order to control all other effects for this demographic characteristic. BMI and complaints suggestive of intermittent claudication were largely responsible for the disappearance (or explanation) of the effect of diabetes on an ABI above 1.4.

Interaction effects

None of the 14 first-order interaction effects – containing diabetes mellitus and one of the other 14 characteristics from Table 1 – showed a statistically significant relationship

with high ABI. So, diabetes effects could not be proven to be different within any of the subcategories of all other 14 predictors of a high ABI, whether they had statistically significant effects on a high ABI or not.

For second-order interactions (diabetes mellitus combined with all pairs between the other 14 patient characteristics), 91 possible effects were tested. Three of them showed stable and statistically significant effects on the presence of a high ABI: BMI, smoking and systolic blood pressure (Table 2). This indicates that the higher the BMI, the lower the possibility for a high ABI and the higher the systolic blood pressure, the higher the possibility.

Overall, the resulting final model contains three second-order effects containing diabetes mellitus (n=9,472), and four direct effects not containing diabetes: complaints of intermittent claudication, a high BMI, a high systolic blood pressure and smoking behaviour.

Discussion

Although it is commonly assumed that the presence of diabetes is related to a high ABI^{16-18,24}, we were not able to show a direct relation between the presence of diabetes and a high ABI, despite a substantial number of patients with an ABI above 1.4 (n=664, 5.2% of the entire cohort). Moreover, in subpopulations, none of the first-order interaction effects between diabetes and another vascular risk factor showed a statistically significant effect on the presence of a high ABI. Finally, we were able to identify three stable and statistically significant second-order interaction effects between diabetes and two other vascular risk factors on the measurement of a high ABI. The strongest effects were seen in middle-aged men and elderly women, men with a diastolic blood pressure above 83 mmHg, and in men with a history of cerebrovascular disease.

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Overall the results of our analyses support the opinion of the TransAtlantic Inter-Society Consensus (TASC) that the frequency of incorrect pressure measurements in diabetic patients due to medial calcification has probably been overestimated in the past.²⁵ Besides, it has been reported that ankle pressure measurements in diabetic patients may be only 5% or 10% too high.²⁴ This means that when atherosclerosis would be present, the ABI might be in the normal range instead of below 0.9, but not above 1.4. It appeared that medial arterial calcification was present in 8.6% of patients with ankle systolic pressures below 100 mmHg, whereas one third of all patients with medial arterial calcification had an ABI of less than 1.0.²⁶

Several limitations of the ABI have been described, which might contribute to the measurement of a high ABI. First, patients with longstanding renal failure or diabetes may have medial calcinosis of the popliteal and tibial arteries. Such calcified arteries may be inadequately compressed by the ankle pressure cuff, resulting in a falsely

elevated ankle pressure and ABI.^{16;27-30} Indeed, it has been shown that ankle pressures of 190 mmHg or higher were highly specific for the presence of medial arterial calcification with a specificity of more than 90%, whereas the sensitivity of ankle systolic pressures to detect the presence of medial arterial calcification decreased from 43.2% downwards.²⁶

Strengths and limitations of the study

This population-based study was performed in a large number of general practices and included a large number of subjects. Therefore, we believe that our findings are valid, relevant, and applicable to patients seen in primary care.

The presence of hypertension, hypercholesterolemia and diabetes were based on a single measurement or on the previously established diagnosis of the general practitioner. No verification according to the criteria of established guidelines was performed.^{19;21;31} Possible misclassification could have occurred, resulting most likely in the underestimation of the role of the particular risk factors with respect to the prevalence of a high ABI. However, in case of an important relation between diabetes and a high ABI, we strongly believe that we should have been able to detect such a relation.

It should be realised that no corrections in the p-value were made, despite the multiple interaction analyses. Therefore, ideally our results require confirmation in another population cohort.

Another finding suggesting that caution should be exerted when interpreting the findings, is that a larger effect for adequately treated diabetes compared to non-adequately treated diabetes was observed in the subgroup of men with a median diastolic blood pressure above 83 mmHg.

Conclusion

Adjusting for potential confounders, we did not find a statistically significant direct relation between the presence of diabetes mellitus and the measurement of a high ABI. Effects of the presence of diabetes mellitus on a high ABI could be found in particular subpopulations, whereas the strongest effects were found in elderly women and in men with an increased diastolic blood pressure or with prior cerebrovascular disease. Based on the absence of an important direct association between the presence of diabetes mellitus and a high ABI in this large population based study, the concept that a high ABI is often caused by diabetes mellitus is not supported.

Table 1: Univariate relationships between high ABI and patient demographic and clinical characteristics (n=12,886).

		n	% ABI>1.4	Chi-square	p-value	OR (95% CI)
Age	55-67 years	6,293	5.8	11.61	<0.001	0.98 (0.97-0.99)
	> 67 years	6,593	4.7			
Gender	Female	6,051	4.0	35.57	<0.001	1.63 (1.38-1.92)
	Male	6,600	6.3			
bmi	≤ 26.8	6,187	4.2	24.07	<0.001	1.05 (1.03-1.07)
	> 26.8	6,241	6.1			
Smoking	Never	4,586	6.1	46.25	<0.001	--*
	Ever	4,364	5.8			0.96 (0.80-1.14)
	Currently	3,612	3.1			0.50 (0.40-0.63)
Hypertension	No	2,497	7.4	50.28	<0.001	--*
	Adequately treated	2,867	5.9			0.77 (0.62-0.96)
	Inadequately treated	7,108	3.9			0.51 (0.42-0.62)
Diabetes	No diabetes	7,261	4.7	8.63	0.013	--*
	Adequately treated	720	5.3			1.14 (0.81-1.61)
	Inadequately treated	4,539	5.9			1.28 (1.09-1.51)
Hypercholesterolemia	No	5,225	5.1	1.020	0.600	--*
	Adequately treated	1,610	5.7			1.12 (0.88-1.43)
	Inadequately treated	5,139	5.1			0.99 (0.83-1.17)
Complaints of IC	No	7,914	5.8	21.78	<0.001	0.67 (0.56-0.79)
	Yes	4,706	4.0			
Family history	No	8,106	5.3	0.727	0.394	0.93 (0.79-1.10)
	Yes	4,780	4.9			
CHD	No	10,257	5.2	0.060	0.807	0.98 (0.80-1.19)
	Yes	2,629	5.1			
Stroke or TIA	No	11,825	5.2	0.059	0.808	0.97 (0.72-1.29)
	Yes	1,061	5.0			
DBP	≤80 mmHg	5,496	5.3	5.402	0.020	0.99 (0.98-1.00)
	>80mmHg	5,721	4.4			
SBP	≤150 mmHg	6,588	6.0	42.330	<0.001	0.98 (0.98-0.99)
	>150 mmHg	4,658	3.3			
HHC	No	12,765	5.2	0.010	0.922	0.96 (0.42-2.19)
	Yes	121	5.0			
Location of complaints	No complaints	5,058	6.4	24.001	<0.001	--*
	Left leg	1,475	4.5			0.69 (0.53-0.90)
	Right leg	1,346	4.4			0.67 (0.51-0.90)
	Both legs	4,970	4.4			0.67 (0.56-0.80)

ABI: ankle brachial index; OR: odds ratio; CI: confidence interval; BMI: body mass index; IC: intermittent claudication; CHD: coronary heart disease; TIA: transient ischemic attack; DBP: diastolic blood pressure; SBP: systolic blood pressure; HHC: hyperhomocysteinemia; *Reference

Table 2: Final logistic regression model using backward elimination procedure

Effect	Chi-square	Degrees of freedom	p-value
BMI	32.70	1	<0.001
Complaints of intermittent claudication	11.19	1	0.001
Smoking	33.27	2	<0.001
Systolic blood pressure	44.22	1	<0.001
DM * Gender * Age	9.83	2	0.007
DM * Gender * Diastolic blood pressure	6.86	2	0.032
DM * Gender * History of cerebrovascular disease	6.31	2	0.043

BMI: body mass index; DM: diabetes mellitus

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PART TWO

CONSERVATIVE

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Medical management of peripheral arterial disease

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Abstract

Introduction: Whether symptomatic or not, peripheral arterial disease (PAD), atherosclerosis in the arteries of the lower extremities, is a common disorder in the general population. The prevalence increases with age and under the influence of vascular risk factors. The most classic symptomatic expression of PAD is intermittent claudication. However, the majority of patients with PAD is asymptomatic or has leg symptoms other than classic intermittent claudication. Both symptomatic and asymptomatic subjects with PAD have increased mortality rates, mainly due to cardiovascular and cerebrovascular expressions of atherosclerotic disease.

Methods: This review focuses on the current available medical therapies for PAD, including risk-factor modification and antiplatelet therapies, as well as strategies for symptomatic relief in both patients with intermittent claudication and patients with critical limb ischemia.

Results and conclusion: In general, risk factor modification and antiplatelet therapy is essential in all patients with PAD to prevent systemic atherosclerotic complications. Furthermore, for symptomatic relief exercise therapy is the main intervention, while pharmacological treatment should be only complementary. In patients with critical limb ischemia, when revascularization therapy is not possible, an attempt should be made to avoid amputation with conservative treatment using analgesics, vasodilators and/or anticoagulants. In case of an acute onset of critical limb ischemia, thrombolysis is indicated.

Introduction

Atherosclerosis is a systemic disease that is most frequently associated with fatal and non-fatal myocardial infarction, stroke, and disease of the aorta and lower extremities. Peripheral arterial disease (PAD), atherosclerosis in the arteries of the lower extremities, whether symptomatic or not, is a common disorder in the general population. The prevalence of PAD increases with age and the presence of vascular risk factors. The estimated overall prevalence of PAD among people of 55 years or older varies between 9% and 23%.¹ The incidence of PAD measured in an open population is 9.9 per 1000 people per year.² Due to ageing of the population in western societies, the prevalence of PAD will rise and the medical treatment will become increasingly important.

The majority of patients with PAD is asymptomatic or has leg symptoms other than classic intermittent claudication, which is defined as leg pain usually involving one or both calf's that arises by walking and is relieved only by rest. It is estimated that only 22% of patients with PAD have these symptoms.³ Elderly male patients with diabetes are especially more likely to have asymptomatic PAD.⁴ The overall annual incidence of symptomatic PAD, with typical intermittent claudication, is 1.5–2.6 per 1000 men and 1.2–3.6 per 1000 women.⁵

Of the patients with asymptomatic PAD, only 5–10% will develop symptomatic PAD in a period of over 5 years.⁶ The majority of patients with intermittent claudication as the clinical symptom of PAD can remain stable over many years. Approximately 15% of these patients develop critical leg ischemia, with ulcerations and rest pain and a high risk for amputation. The annual incidence of critical limb ischemia is estimated to be 0.25–0.45 per 1000 persons.^{7,8} Of the patients with critical limb ischemia, between approximately 20 and 45% will require an amputation of the leg.⁹

Although the rate of local symptoms and complications might seem low, PAD should be considered as a serious disease because of the high morbidity and mortality due to other atherosclerotic manifestations, namely stroke and myocardial infarction.

Approximately 30% of the symptomatic patients will die within 5 years due to vascular diseases and 5–10% due to a non-vascular cause.^{10–12} There is even a trend towards an increased total as well as cardiovascular mortality in patients with asymptomatic PAD.^{6,13,14}

Treatment of PAD is aimed to reduce the clinical symptoms of intermittent claudication, to prevent or reduce local tissue loss, and to prevent general complications, such as coronary heart disease and cerebrovascular disease. This review will focus on vascular risk factor modification and antiplatelet therapies for patients with both symptomatic and asymptomatic PAD, as well as on currently available strategies for relief of symptomatic PAD.

Risk factor modification

The first priority in treatment of patients with PAD is to try to adjust the known vascular risk factors to decrease the progression of atherosclerosis and to prevent the development of atherothrombotic complications. Modifiable risk factors for atherosclerosis include smoking, hypertension, diabetes mellitus, hyperlipidemia, and an elevated homocysteine concentration.

Smoking cessation

Smoking behavior is associated with a considerably increased risk of symptomatic PAD.¹⁵ Symptoms of PAD arise approximately a decade earlier in smokers than in non-smokers, whereas smokers with PAD have amputation rates twice as high as those who have never smoked.⁹ There are suggestions that smoking cessation will decrease the risk for critical leg ischemia, and reduces the mortality in patients with PAD.^{16,17} Smoking cessation is considered to be a critical step in risk factor management. Although smoking cessation probably reduces the severity of claudication, a meta-analysis concluded that it did not significantly improve the walking capacity.¹⁸

There are several possible strategies to support the cessation of smoking. The two-year cessation rate of a plain oral or written advice from a physician is as low as 13%¹⁹, although this is a relative increase of approximately 30% as compared to no intervention.²⁰ Interestingly, a Cochrane review describing 14 studies concerning over 5000 people, demonstrated that a strategy of counseling, including a first counseling of at least 10 minutes, followed by repeated appointments by telephone, is more effective than a short oral or written advice, with an odds ratio (OR) of 1.62 (95% confidence interval (CI): 1.35–1.94).²¹ Similar effects were visible in group behavior therapy programs for smoking cessation.²² On the contrary, a single, relatively small study in patients with PAD, which was not included in the Cochrane review, failed to demonstrate this effect.²³ In the medical support of smoking cessation strategies, nicotine replacement showed to be a safe and effective approach.^{24–28} There is no clear evidence to support the superiority of any particular nicotine replacement therapy, formulation, or dose (e.g. patch, gum, spray, inhaler, sublingual tablet).²⁹ Bupropion, an antidepressant drug, has shown to be beneficial in smoking cessation therapy for patients with PAD, with statistically significant higher long-term abstinence rates of 18.4%³⁰ compared to placebo (5.6%).^{29–34} Both nortriptyline and clonidine have also been found to be beneficial in the cessation of smoking.²⁴ There is no evidence of effect of alternative therapy (e.g. hypnotherapy, acupuncture, aversive smoking).^{35–37} A combination of pharmacology and counseling achieves the highest rate of smoking cessation.³⁸

Hypercholesterolemia

Lipid modification is associated with stabilization and even regression of femoral atherosclerosis.^{39–42} Although diet and exercise have been found to alter the lipid profile towards a less atherogenic type, many patients require lipid-lowering medications. Statins are effective at reducing LDL-cholesterol levels, causing a significant reduction in all-cause mortality from 14.7% to 12.9% with the use of simvastatine compared to

placebo.⁴³ For the first occurrence of a major vascular event, a relative reduction of 24% (in absolute terms from 25.2% to 19.8%) was found in the Heart Protection Study.⁴³ Lowering the total cholesterol and LDL by 25% with a statin reduces cardiovascular mortality and morbidity in patients with PAD by approximately 25% (relative), irrespective of age, sex, or baseline cholesterol concentration.⁴³ Simvastatin significantly reduces the incidence of new intermittent claudication by 38% compared with placebo (in absolute terms from 3.6% to 2.3%) over six years in patients with hypercholesterolemia and coronary heart disease.⁴⁴ Moreover, both simvastatin and atorvastatin significantly increased the pain free walking distance after one year of treatment with 63%, compared to 38% with placebo.^{45,46} This effect is most likely to be independent of the effects on serum lipid measurements due to statin use.^{47,48} Other lipid lowering agents include bezafibrate, which significantly decreases the amount of nonfatal coronary events⁴⁹, nicotinic acid, which reduces the cardiovascular morbidity and mortality⁵⁰⁻⁵², and cilostazol, which has been shown to decrease the plasma triglycerides by 15%.⁵³

Hypertension

Although there are no data available to demonstrate that treatment of hypertension alters the arising of intermittent claudication or the progression of the disease in the peripheral circulation, it is recommended that patients with PAD acquire a blood pressure of less than 130/85 mmHg.^{54,55} A large reduction in blood pressure may initially worsen intermittent claudication, independent of what drug treatment is used. There is no evidence that beta blockers are particularly culpable, as has been suggested previously.^{56,57} ACE inhibitors showed significantly greater hemodynamic improvements in the extremity in which baseline blood flow is decreased by limb arterial atherosclerosis compared with either calcium channel blockers or beta blockers.^{58,59} Furthermore, ACE therapy is associated with improvements in both the pain free walking distance (from approximately 170 to 210 meters), the maximal walking distance (from approximately 230 to 270 meters)⁶⁰, and with significant improvements in either the ankle systolic pressure or the ankle brachial index (from 0.59 to 0.64).⁵⁹⁻⁶¹ The evidence of the effectiveness of calcium channel antagonists and angiotensin II receptor agonists is poor, and therefore it remains unclear whether significant benefit or risk accrues from their use.⁵⁷

Diabetes mellitus

Diabetes mellitus is highly associated with PAD and its progression.^{62,63} Rigorous control of blood glucose prevents the micro-vascular complications of diabetes, although similar benefits on the macro circulation have not been ascertained.⁶⁴ Intensive therapy, achieving a HbA1c of below 7%, elicited a trend for reduced risk of non-fatal cardiovascular events by 41% (from 0.8 to 0.5 events per 100 patients -years)⁶⁴, but had no effect on the risk of death or amputation due to PAD.⁶⁴⁻⁶⁷ It has been estimated that for every 1% increase in HbA1c there is a 28% ($p < 0.002$) increased risk of death, independent of age, blood pressure, serum cholesterol or smoking status.⁶⁸

Furthermore, each 1% increase in HbA1c was associated with a 28% increase in risk of incident PAD.⁶⁵

Hyperhomocysteinemia

Several reports have shown a strong association between increases in plasma homocysteine concentration and PAD.^{69,70} However, there are currently no trials available on the treatment of hyperhomocysteinemia in patients with PAD.⁷¹ The level of homocysteine can significantly be reduced by administration of folate, vitamin B6, and vitamin B12.^{72,73} Nevertheless, no randomized trial has been able to demonstrate that reducing serum homocysteine concentration is beneficial in patients with PAD⁷⁴, although an increased level of homocysteine is associated with an increased risk of death from cardiovascular causes.⁷⁰

Antiplatelet therapy

In addition to modification of vascular risk factor(s), antiplatelet therapy must be considered. There is strong evidence that antiplatelet agents reduce major cardiovascular events over an average of about two years compared with control treatment.^{75,76} Besides, systemic reviews have found that antiplatelet agents reduce the risk of arterial occlusion and revascularization procedures compared with placebo or no treatment.^{18,76} The benefits of antiplatelet therapy are not influenced by gender and age, or by the presence of hypertension or diabetes.⁷⁶ Based on the available evidence, the first-line antiplatelet therapy should be aspirin (160–325 mg/d) or clopidogrel (75 mg/d) when aspirin is contraindicated or not tolerated.⁷⁷

Aspirin

Antiplatelet therapy with aspirin in patients with PAD showed a significant reduction of 23% (in absolute from 7.1% to 5.8% over an unspecified period) in subsequent serious cardiovascular events, with similar benefits among patients with intermittent claudication.^{75,76} Large randomized trials have shown that aspirin delays the progression of established PAD, as assessed by serial angiography, and consequently decreases the need for surgical revascularization with a relative risk of 0.54 (95% CI 0.30–0.95) compared to placebo.^{78,79} Interestingly, up to 25% to 40% of individuals have a reduced pharmacological response to aspirin, although without established clinical relevance.^{80,81}

Clopidogrel

Clopidogrel is a thienopyridine antiplatelet and associated with less gastrointestinal hemorrhage and other upper gastrointestinal upset compared to aspirin.⁸² It showed a 23.8% (from 8.9 to 36.2) risk reduction in the average event rate per year as compared with the use of aspirin in patients with PAD.⁸³ Overall, including patients with myocardial infarction and stroke, the relative risk reduction was 8.7% (95% CI: 0.3–16.5)⁸³, with an odds reduction of 10% for myocardial infarction, ischemic stroke, and vascular death.⁸⁴ When treatment effects on non-vascular deaths are not considered,

lifetime treatment duration of clopidogrel in patients with PAD is more cost-effective than aspirin. Otherwise, it is cost-effective during the first two years of treatment.⁸⁵ Compared with ticlopidine, another thienopyridine, clopidogrel is equally effective, except with markedly less negative side effects. Since ticlopidine has been associated with life-threatening hematological reactions, this drug is not longer used.²⁶

Although there is little evidence, a combination of antiplatelet therapy with aspirin and clopidogrel could be initiated if a patient experiences a second vascular event while receiving mono-therapy.^{77,86} The involved physician should be aware of a prolonged bleeding time during a combination antiplatelet therapy.⁸⁷

Other antiplatelet agents and anticoagulants

There is no evidence that dipyridamole, as mono-therapy or combined with other antiplatelet agents, reduces the risk of vascular death, though it may reduce the risk of further vascular events.⁸⁸

Neither is there evidence to support the routine use of warfarin in patients with intermittent claudication who show sinus rhythm.⁸⁹

Symptomatic relief of PAD

Intermittent claudication

Exercise therapy

Exercise therapy is a highly efficacious therapy for the treatment of PAD.⁹⁰ Comparing exercise therapy to a control group, a significant improvement in walking distance was present in the exercise group, with an overall improvement in maximal walking ability of approximately 150% (range 68%–230%).⁹⁰ A Cochrane review in preparation shows a significant improvement in walking distance in patients receiving a supervised exercise therapy program, compared to a non-supervised program, with a prolonged maximal walking distance of approximately 300 meters after 6 months.^{91,92} This indicates that supervised exercise therapy is preferred as the main symptomatic treatment of patients with intermittent claudication. A meta-analysis of exercise programs for intermittent claudication demonstrated that exercise therapy to near-maximal pain for at least six months was most beneficial in improving claudication symptoms.⁹³ An important instruction for patients during a supervised exercise program is therefore the reassurance that walking through the claudication pain not only does no harm, but will in fact gradually increase the walking distance. Interestingly, exercise therapy has no effect on the ankle brachial index or on collateral vessel growth.^{90,94}

Secondary to the advantage on symptomatic relief of PAD, exercise therapy has been found to yield beneficial effects on the development and decrease of hypertension, diabetes mellitus, obesity, and lipoprotein profiles.⁹⁵

Pentoxifylline

It is suggested that pentoxifylline, through a variety of pharmacological effects, may have a small effect on walking ability, although the available data are insufficient to

Critical limb ischemia

Revascularization is the therapy of choice in patients with critical limb ischemia.⁹ However, when this is not possible, conservative treatment, with analgesics, vasodilators and/or anticoagulants is obligatory in an attempt to avoid amputation.

Prostanoids

Prostanoids might have beneficial effects on wound healing, limb loss, and survival in patients with critical limb ischemia.⁹ The currently available data support the use of iloprost in patients who are unsuitable for any procedure or in whom revascularization attempts have failed.⁹

Antiplatelets and anticoagulants

Long-term treatment with aspirin and ticlopidine has been shown to reduce the progression of femoral atherosclerosis.¹²¹ Anticoagulant treatment with low-molecular-weight heparin showed positive results with a decrease in rest pain and an improvement in healing of ulcers previously resistant to treatment.¹²² No clinical trials have been published on the use of unfractionated heparin for critical limb ischemia. The results of the investigated vasoactive drugs for patients with critical limb ischemia are unconvincing or negative, and are not recommended by the TransAtlantic Inter-Society Consensus (TASC).⁹

Gene based therapy

Therapeutic angiogenesis is suggested to be effective in the treatment of critical limb ischemia, improving collateral vessel development with subsequent significant improvement in tissue loss, resolution of rest pain, and lowering the level of amputation.¹²³⁻¹²⁵ This efficacy was associated with clinical objective findings of an improved ankle brachial index with a difference of approximately 0.14¹²⁵, a significant increase in pain-free walking time (from 2.5 minutes to 3.8 minutes at an average of 13 weeks after gene therapy ($p=0.043$)), and blood flow on magnetic resonance angiography.^{123,125}

Both intramuscular vascular endothelial growth factor (VEGF) gene transfer, hepatocyte growth factors plasmid and recombinant fibroblast growth factor (FGF) have shown to be safe, feasible and effective.^{125,126} However, this novel technology is currently not granted for a regular basis and should be reserved for those patients with severe limb threatening ischemia due to PAD that is not suitable or has failed with conventional revascularization.¹²⁷

Another alternative for using therapeutic angiogenesis is bone marrow mononuclear cell therapy. The bone marrow cells have a natural ability to supply endothelial progenitor cells and to secrete various angiogenic factors or cytokines. In a small randomized trial the ankle brachial index significantly improved with a difference of 0.09 (95% CI: 0.06-0.11), the transcutaneous oxygen pressure increased from 28.8 to 46.3, and the pain free walking distance significantly improved by about 3.5 minutes 24 weeks after injection with bone marrow mononuclear cells.¹²⁴ Besides these ischemic

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Acute limb ischemia

In acute limb ischemia, an acute onset due to an embolic or thrombotic occlusion, thrombolysis is indicated. Two meta-analysis in patients with acute limb ischemia concluded that there is an equal mortality (RR 1.24; 95% CI: 0.80–1.90) and amputation rate (RR 0.89; 95% CI: 0.58–1.38) between patients treated with thrombolysis or surgery. The need for open major surgical procedures on the other hand is reduced after thrombolysis, although with a higher rate of bleeding (RR 2.9; 95% CI: 1.1–7.9) and distal embolization (OR 8.4; 95% CI: 4.5–15.6).^{129, 130} Urokinase and recombinant tissue-type plasminogen activator are most widely used agents. Both agents reported a similar efficacy and safety level in the STILE study¹³¹, although thrombolysis using low dose tissue plasminogen activator has a shorter duration and therefore provides a significant overall cost reduction.¹³²

The combination of eptifibatide and tenecteplase showed to be a viable option in the treatment of acute limb ischemia. In a small study, a high immediate clinical and technical success was demonstrated, as well as an acceptable 3-month clinical outcome, without any cases of death, intracranial hemorrhage, or remote-site bleeding.¹³³ Fibrinogen levels decreased to a greater degree than studies using tenecteplase alone, but this was not associated with any clinical results. Abciximab, which prevents the binding of fibrinogen, and by this means inhibiting platelet aggregation, is also used as adjuvant therapy for thrombolysis.¹³⁴ This treatment was associated with a reduced need for hospitalization, interventions, and amputations and also markedly shortened the duration of clot lysis in comparison with aspirin.¹³⁵ However, glycoprotein IIb-IIIa receptor blockers showed no effect in reducing the incidence of major cardiovascular events.^{136,137} It is reported that thrombolysis occurred faster using a combination of urokinase and abciximab compared to urokinase alone, although with a higher rate of nonfatal major bleeding.¹³⁸

Conclusion

In all patients with PAD both risk factor modification and antiplatelet therapy are important therapies to prevent or reduce local tissue loss, and to prevent general complications, such as coronary heart disease and cerebrovascular disease. Pharmacological treatment should not replace exercise therapy programs and other lifestyle adjustments in patients with intermittent claudication, but plays an important role as adjunctive treatment when invasive therapy is not suitable, or for those who have not sufficiently benefited from exercise therapy. When revascularization therapy is not possible in patients with critical limb ischemia, conservative treatment, with analgesics, vasodilators and/or anticoagulants is essential for symptom relief and an attempt to avoid amputation. Finally, in the patient population with an acute onset of critical limb ischemia due to an embolic or thrombotic event, thrombolysis is indicated.

Table 1: Components of best medical treatment for secondary prevention

Component	Agent	Effect on morbidity and mortality	Effect on PAD	Effect on walking distance	Effect on ABI
Smoking cessation	Advice	Possible reduction of MI and cardiac death			
	Nicotine replacement		-	-	-
	Bupropion				
Reduction in cholesterol	Statin	25% reduction after cholesterol reduction with 25%, 12% reduction of total mortality, 17% reduction of vascular mortality rate. 24% risk reduction for the first major CVE	38% reduction of incidence of intermittent claudication, beneficial effects on endothelial function and vascular inflammation	63% increase in pain free walking distance after one year of treatment.	-
	Fibrates	Significant decrease of non-fatal CVE	-	-	
Blood pressure lowering	Beta-blockers	53% reduction of new CVE	-	-	-
	ACE-inhibitors	22% risk reduction	Increase in blood flow velocity	24% improvement of pain free walking distance, 17.4% increase of maximal walking distance	Significant improvement from 0.59 to 0.64
Treatment of Diabetes		Risk reduction of 41% for CVE	-	-	-
Antiplatelet	Aspirin	23% general reduction, 54% risk reduction for peripheral revascularization	-	-	-
	Clopidogrel	23.8% risk reduction	-	-	-

PAD: peripheral arterial disease; ABI: ankle brachial index; MI: myocardial infarction; CVE: cardiovascular event

Table 2: Components of best medical treatment for symptomatic relief of PAD

Component	Agent	Effect on morbidity and mortality	Effect on PAD	Effect on walking distance	Effect on ABI
Exercise therapy	Supervised regimen	25% reduction in cardiovascular mortality	-	150% improvement	-
Cilostazol		-	-	28-100% improvement	Significant improvement from 0.64 to 0.70
Prostanoids		-	Beneficial for wound healing, limb loss, and survival	-	-
Anticoagulants	Low-molecular-weight heparin	-	Decrease of rest pain, healing of ulcers	-	-
Gene based therapy		-	Significant beneficial effects on tissue loss, resolution of rest pain, lowering the level of amputation	Significant increase from 2.5 to 3.8 minutes in pain free walking time.	Improvement with approximately 0.14
Pain relief	Spinal cord stimulation	-	Beneficial effect on limb salvage, ulcer healing, and pain relief	-	-

PAD: peripheral arterial disease; ABI: ankle brachial index

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7

Supervised exercise therapy versus non-supervised exercise therapy for intermittent claudication

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Abstract

Introduction: Although exercise therapy is considered to be of significant benefit to people with leg pain (intermittent claudication), almost half of those affected do not undertake any exercise therapy.

To evaluate the effects of supervised versus non-supervised exercise therapy on the maximal walking time or distance for people with intermittent claudication.

Methods: The Cochrane Peripheral Vascular Diseases Group searched their Specialized Register (last searched November 2005) and the Cochrane Central Register of Controlled Trials (CENTRAL) database in The Cochrane Library (last searched Issue 4, 2005). In addition, we handsearched the reference lists of relevant articles for additional trials. There was no restriction on language of publication. Randomized and controlled clinical trials comparing supervised exercise programs with non-supervised exercise programs for people with intermittent claudication. For all continuous outcomes we extracted the number of participants, the mean differences, and the standard deviation. If data were available, the standardized mean difference was calculated using a fixed-effect model.

Results: We identified twenty-seven trials, of which 19 had to be excluded because the control group received no exercise therapy at all. The remaining eight trials involved a total of 319 male and female participants with intermittent claudication. The follow up ranged from 12 weeks to 12 months. In general, the supervised exercise regimens consisted of three exercise sessions per week. All trials used a treadmill walking test as one of the outcome measures. The overall quality of the included trials was good, though the trials were all small with respect to the number of participants, ranging from 20 to 59.

Supervised exercise therapy showed statistically significant and clinically relevant differences in improvement of maximal treadmill walking distance compared with non-supervised exercise therapy regimens, with an overall effect size of 0.58 (95% confidence interval 0.31 to 0.85) at three months. This translates to a difference of approximately 150 meters increase in walking distance in favor of the supervised group.

Conclusions: Supervised exercise therapy is suggested to have clinically relevant benefits compared with non-supervised regimens, which is the main prescribed exercise therapy for people with intermittent claudication. However, the clinical relevance has not been demonstrated definitely and will require additional studies with a focus on the improvements in quality of life.

Background

Intermittent claudication is the main symptom of peripheral arterial disease (PAD) and is defined as leg pain in the calf of one or both legs that occurs by walking, and is relieved only by rest. The prevalence of intermittent claudication in an open study population varies between 1.6% to 4.5%.¹⁻⁴

The primary and most effective treatment for people with intermittent claudication is exercise therapy⁵ which was first suggested by Erb.⁶ In 1966 the first randomized controlled trial of exercise therapy in patients with peripheral arterial disease demonstrated an obvious improvement in treadmill walking ability.⁷ In a Cochrane systematic review of randomized clinical trials, Leng et al⁸ described an overall improvement in maximal walking ability of approximately 150%, ranging from 68%⁹ to 230%¹⁰ associated with exercise therapy, compared with no exercise therapy, medical, or surgical therapy. However, the exercise programs included in this meta-analysis vary widely, ranging from a physician recommending unsupervised walking in the community, to a formal supervised exercise program involving walking on a treadmill.

Currently, exercise therapy in a supervised, centre-based setting is only available in a few centres.¹¹ In the Netherlands for instance, the current prescription of exercise therapy consists usually of a single “go home and walk” advice by the general practitioner, sometimes with an additional brochure. It is reported that exercise therapy is not undertaken by almost half of the people who have intermittent claudication, whereas the most important barrier for performing walking exercise is a lack of supervision.¹² However, in a Cochrane review about functional activity, longer lasting benefits of non-supervised, home-based exercise programs compared with supervised centre-based programs were described, due to better adherence rates in home-based exercise programs.¹³

Recently, some studies comparing supervised exercise therapy with non-supervised exercise therapy have been published. It is suggested that supervised exercise programs are more effective compared with non-supervised programs. To determine the optimum form of exercise therapy treatment in daily practice, a meta-analysis was performed to assess the effects on walking distance of supervised exercise programs compared with non-supervised exercise programs in people with intermittent claudication.

Objectives

The main objective of this review was to evaluate the effects of supervised versus non-supervised exercise therapy on the maximal walking time or distance for people with intermittent claudication.

Criteria for considering studies for this review

Types of studies

Randomized clinical trials and controlled clinical trials comparing supervised exercise programs with non-supervised exercise programs were considered for this review. Trials that were not analyzed on an intention-to-treat basis were included, provided all randomized participants were accounted for.

Types of participants

Patients with intermittent claudication (Fontaine II)⁴⁶ due to atherosclerotic disease, diagnosed either by questionnaire or clinically, who were considered for conservative treatment, were included. Studies of patients with asymptomatic lower limb atherosclerosis identified by testing were excluded.

Types of interventions

All trials comparing a supervised with a non-supervised exercise therapy program in the treatment of intermittent claudication were included. Trials in which the control group did not receive exercise were excluded. Trials comparing three or more different therapy programs, supervised and non-supervised therapy programs with other kind of programs, were included. Of these trials only the subjects treated by supervised or non-supervised exercise therapy were taken into account. More than 50% of the time spent in a supervised exercise therapy program needed to consist of walking. Inclusion of trials were not limited by the duration, frequency or intensity of the exercise program.

Types of outcome measures

The primary outcome measure was the effect on the maximal treadmill walking distance or time.

The following secondary outcome measures were also considered:

- pain-free treadmill walking distance, or time
- mortality
- compliance
- functional status
- quality of life

Search methods for identification of studies

The Cochrane Peripheral Vascular Diseases Group searched their Specialized Register (last searched November 2005) and the Cochrane Central Register of Controlled Trials (CENTRAL) database in The Cochrane Library (last searched Issue 4, 2005) for publications describing randomized controlled trials of supervised exercise therapy versus non-supervised exercise therapy. The PVD Group Specialized Register contains citations of trials identified through regular electronic searches of MEDLINE (1966 to date) and EMBASE (1980 to date), and through handsearching journals and conference proceedings. The full list of journals that have been handsearched, as well as the search strategies used are described in the 'Search strategies for the identification of studies' section within

the editorial information about the Cochrane PVD Group in The Cochrane Library. In addition, we handsearched the reference lists of papers identified from the searches for potential trials. There was no restriction on language of publication. See Table 01 for the strategy used to search CENTRAL in The Cochrane Library.

Methods of the review

Selection of trials

Two authors (BB and EMW) independently selected trials for this review. Two authors (JT and MP) confirmed the suitability of selected trials for inclusion in the review. Where necessary, additional information was sought for included trials.

Quality of trials

One author (BB) assessed, and one author (MP) confirmed the methodological quality of the trials primarily for the adequacy of the allocation concealment and follow up. Obviously in trials that compare exercise programs with walking distance as the primary outcome, blinding is not possible and therefore was not considered.

We gave each trial an allocation score A (clearly concealed), B (unclear if concealed) or C (clearly not concealed) and a summary score of A (low risk of bias), B (moderate risk of bias) or C (high risk of bias), according to the criteria in the Cochrane Collaboration Handbook (Mulrow 1997). For each trial, we extracted the number of participants originally allocated to each treatment arm from the data and we performed an intention-to-treat analysis.

Data extraction

Two authors (BB and EMW) independently extracted data and entered the data into Review Manager 4.2. We resolved disagreements by discussion. For all continuous outcomes (i.e. walking distance or walking time, compliance, and quality of life) we extracted the number of participants, the mean difference, and the standard deviation for each group in the study, if available. We also recorded other details of the included trials for example, the study setting, statistical power, and the number of drop outs in each group.

Statistical analyses

If data were available, we performed statistical analyses using the Review Manager software. We standardized reported data of walking time and distance to effect sizes to enable the calculation of an overall standardized mean difference. For this purpose the difference in outcome of each study was expressed in the standard deviation (SD) observed in this study.¹⁵ We calculated the standardized mean difference (SMD) using a fixed-effect model, as the results were presented on different scales (distance or time).

We used both a chi-square test and a I² test to test the heterogeneity between trial results. We used the tests of heterogeneity at a significance level of alpha = 0.05 to

examine whether the observed variation in study results was compatible with the variation expected by chance alone. Where possible, we pooled trials results by meta-analysis. We analyzed randomized clinical trials separately for the primary outcome measure.

Description of studies

We identified twenty-seven clinical trials on supervised exercise therapy in patients with PAD (Fontaine II).¹⁴ Nineteen trials had to be excluded because the control groups received no exercise therapy at all leaving the remaining eight trials eligible for inclusion. Of these eligible trials, seven were randomized clinical trials^{16–22}, and one was a controlled clinical trial²³. We were able to retrieve the full text of all the eligible trials.

The eight included trials involved a total of 319 participants; 159 received supervised exercise therapy and 160 received non-supervised exercise therapy. The trials were conducted in the United States (3), Denmark (2), UK (2), and Switzerland (1). Six of the trials were relatively recent (1997 to 2005), and two Danish trials were conducted in 1975 and 1977.^{18,19}

The included trials were small, with five containing between 40 and 59 participants^{16,18–20,23}, and three less than 40 participants^{17,21,22}. The largest trial of 59 participants was conducted recently in the UK.¹⁶ In five of the trials to be eligible for inclusion, patients with intermittent claudication had to be stable for several months.^{16,17,20,21,23} This criterion was not mentioned in the other three trials.^{18,19,22} In six trials both males and females were included^{16,17,19,20,22,23}; one trial included only male employees¹⁸, and the final trial included only male participants based on the inclusion of veterans only²¹. The mean age of the participants was 67 years, ranging from 40 to 86 years.

Inclusion criteria

In the three trials that used age restrictions, participants had to be between 40 and 59 years old¹⁸, between 50 and 75 years old²⁰, or 50 years and over²². In one trial¹⁸, the diagnosis of intermittent claudication was based on a clinical history. In the most recent trials¹⁷, participants were included when an occlusion of the superficial femoral artery of ≥ 6 cm in length was found on ultrasound or angiogram, or both. The remaining six trials^{16,19–23} used a low ankle brachial index (ABI) or a drop in ankle pressure after exercise for the diagnosis of intermittent claudication.

Exclusion criteria

The exclusion criteria were variable. In general, ischemic rest pain, comorbid illness with limitations in an exercise therapy program, and recent vascular surgery or percutaneous transluminal angioplasty (PTA), were mentioned. In one study smoking habits²², and in another the presence of diabetes mellitus²¹ was an exclusion criterion. Kakkos excluded patients with a maximal claudication distance greater than 300 meters or less than 50 meters, and cases in which the results of the treadmill test differed

more than 25% in terms of absolute claudication distance from three screening tests were also excluded.¹⁷

Exercise regimens

In general, the supervised exercise programs consisted of three exercise sessions a week for 12 weeks. However, in two trials^{16,17} the supervised program lasted 24 weeks. In addition, in the trial of Cheetham the supervised exercise program was given as a weekly session.¹⁶ Generally, a training session involved walking on a treadmill with a varying intensity until moderate or intense pain occurred, followed by a short period of rest. Three studies^{16,18,20} described an alternative training regimen with walking training as the dominating exercise but with additional exercises of lower limb strengthening. In six of the trials^{16-20,23} the duration of each supervised exercise session varied between 30 and 60 minutes. Two trials^{21,22} described exercise regimens with gradually increasing periods of time. After the supervised exercise program, participants were advised to continue the training session in a home-based setting. In five studies^{16,19,20,22,23}, the outcome measurements were repeated three months after the end of the supervised program and in one study six months after the end of the supervised program¹⁷. In the trial of Patterson²⁰, participants were additionally educated weekly about PAD.

The participants in the non-supervised exercise therapy groups were advised to walk at least three times weekly during 12 weeks with a walking intensity varying between tolerance and intense pain. Two trials extended the supervised exercise regimen with a non-supervised regimen for the period of 12 weeks and 40 weeks respectively.^{19,22} The advised training regimen for the home-based groups consisted of walking as the dominating exercise with an advised duration of each session between 20 and 60 minutes, taking into account that in two regimens, participants were advised to extend the duration from 15 minutes or 35 minutes up to 40 and 55 minutes respectively. The two Danish trials did not give information regarding the contents of the advised training.^{18,19}

Outcome measurements

All trials used a treadmill walking test to measure the pain-free treadmill walking distance or time and the maximal treadmill walking distance or time. The treadmill tests used vary widely and are given in the Table 1. The data of the maximal treadmill walking distance of Cheetham were calculated based on the P value, assuming that the standard deviations of both groups were equal.¹⁶ The data of Patterson were extracted out of the accompanying figures.²⁰

Mortality was registered during the study periods.

Two trials measured the compliance by registering absence in the supervised groups.^{16,23} In the non-supervised groups compliance was based on self reporting log books. Patient-reported outcomes were taken into account in five trials^{16,17,20-22}, whereas the

Medical Outcomes Study (MOS) Short Form (SF) –36 was used in four trials^{17,20–22} and the MOS SF–20 in the trial of Cheetham¹⁶. Additionally, the Walking Impairment Questionnaire (WIQ) was used in two trials^{17,21}, the Intermittent Claudication Questionnaire (ICQ) in one trial¹⁷, and the Charing Cross Claudication Questionnaire (CCCQ) in another trial¹⁶.

Methodological quality of included studies

Seven randomized clinical trials^{16–22} and one controlled clinical trial were included²³. Three randomized clinical trials had an allocation score of A^{16–18}, the remaining four a score of B^{19–22}.

In five trials there was either no loss, or minimal loss to follow up. Two participants withdrew from both groups in the Cheetham trial.¹⁶ However, in the trial of Patterson²⁰, eight participants in the supervised group and nine in the non-supervised group were lost to follow up, of whom two in the supervised group and five in the non-supervised group were lost to follow up before the first control measurement at three months. In the trial of Kakkos, six participants in the supervised group and one in the non-supervised group were lost to follow up.¹⁷ The overall dropout rate was 8%.

Results

1. Primary outcome: Maximal treadmill walking distance

Data for the maximal treadmill walking distance after three months of exercise therapy were available in six trials^{16,18,20–23} with a total sample size of 239, and are shown in Table 2. This outcome was repeated after six months in five trials with 172 participants^{16,17,20,22,23}, after nine months (n=56) in one trial¹⁶, and after 12 months (n=69) in two trials^{16,17}.

We calculated the effect estimates after standardization of the mean differences. At three months the maximal treadmill walking distance was increased with an overall effect size of 0.58 (confidence interval (CI): 0.31 to 0.85; P<0.0001), using the fixed-effect model. This translates to a difference in favour of the supervised group of approximately 150 meters in increased walking distance, corresponding with approximately 30% to 35% difference in increase. At six months this effect was maintained, with an overall effect size of 0.89 (CI: 0.57 to 1.21; P<0.0001).

In the two trials repeating the outcomes, the effect was present at nine months¹⁶, and 12 months after exercise therapy^{16,17}.

We undertook sensitivity analyses by leaving out the single non-randomized controlled clinical trial²³ which resulted in a similar overall effect size (0.51; 95% CI: 0.22 to 0.81; P=0.0006).

At three months there was a significant heterogeneity, with a Chi-squared test of 18.84 (P=0.002) and an I² of 73.5%. However, using the random-effects model for the results after three months resulted in a similar overall effect size (0.61; 95% CI: 0.07 to 1.14;

$P=0.03$). This heterogeneity is likely due to the early negative trial of Nielsen¹⁸ which contrasts with the later positive trials. At other time points there was no evidence of heterogeneity.

2. Pain-free treadmill walking distance

Data for pain-free treadmill walking distance after three months of exercise therapy were available in five trials¹⁹⁻²³ with a total sample size of 182 (Table 3). This outcome was repeated after six months in four trials ($n=116$)^{17,20,22,23}, and at 12 months after exercise therapy in two trials^{17,19} ($n=52$).

At three months the pain-free treadmill walking distance was increased with an overall effect size of 0.61 (CI: 0.31 to 0.91; $P<0.0001$). This translates to a difference in increased walking distance in favor of the supervised group of approximately 125 meters.

At six months this effect was maintained, with an overall effect size of 0.83 (CI: 0.44 to 1.21; $P<0.0001$). The two trials that measured this outcome at 12 months^{17,19}, showed no significant difference between both groups.

We undertook sensitivity analyses by leaving out the single non-randomized controlled clinical trial²³ which resulted in a similar overall effect size (0.54; 95% CI: 0.20 to 0.88; $P=0.0002$). There was no statistical heterogeneity at three months ($P=0.13$), six months ($P=0.24$), or 12 months ($P=0.64$).

3. Mortality

In three of the eight trials^{16,17,20}, a total of five participants died during the course of the study. In the trial of Patterson 1997, nothing is mentioned about the cause of death of the two participants who died during follow up (both from the supervised group).²⁰ Cheetham 2004 registered two deaths (one from each group), neither of them were attributed to a vascular event.¹⁶ In the most recent trial, the cause of death of the one person who died was acute leg ischemia after an operation for bladder cancer.¹⁷ No deaths occurred during the study period in the remaining trials.

4. Compliance with exercise

Two trials^{16,23} looked at the compliance for exercise training. Degischer based the analysis of compliance in the non-supervised exercise therapy group on logbook entries and a weekly telephone interview.²³ Compared with the supervised group, where the amounts of training sessions were quoted, no difference in compliance to the training program was measured. Cheetham 2004 simply asked participants whether they walked 'less than three times', 'three times' or 'more than three times' a week.¹⁶ Twice as many participants in the supervised exercise therapy group claimed to be walking over three times a week compared with the non-supervised group.

5. Patient-reported outcomes

Four trials^{16,17,20,22} used the MOS SF-36 and Regensteiner²¹ used the MOS SF-20. The WIIQ was used in two trials^{17,21}, the ICQ in the trial by Kakkos¹⁷, and the CCCQ was used by Cheetham et al¹⁶.

While frequently a difference before and after training within a group was found, only one trial reported a borderline statistically significant difference between the improvement in the two exercise regimens over a 12 months period ($P=0.02$), in the domain 'Physical Functioning' using the MOS SF-36.¹⁶ Using the CCCQ a statistically significant difference between the two groups ($P<0.05$) was found after nine months of exercise in favor of the supervised exercise therapy group.¹⁶ Intragroup analyses of the WIIQ and ICQ showed less improvement or even reduction in the non-supervised group compared with an increase in score in the supervised group.^{17,21} However, the changes were not compared between the groups.^{17,21}

Discussion

The eight trials included in this review all involved a small number of patients, but despite this, statistically significant and clinically relevant differences in improvement in walking distance were consistently demonstrated in favour of supervised exercise therapy compared with non-supervised exercise therapy regimens.

Despite the variability of the prescribed exercise regimens and treadmill walking tests used to measure the outcome, heterogeneity was only present for the results of the maximal treadmill walking distance after three months. This is likely due to the early negative trial of Nielsen¹⁸, which contrasts with the later positive trials. Indeed removing this trial from the analysis results in the absence of statistical heterogeneity. Next to chance alone, there are several factors that could contribute to the observed heterogeneity. First, the participants of the Nielsen trial¹⁸ were remarkably younger (40 to 59 years) compared with participants of the other trials^{16,17,20-23} (mean age of 67.4 years). Furthermore, in the trial of Nielsen¹⁸ no treadmill walking was used during training sessions. However, Cheetham et al also did not use treadmill walking during training sessions.¹⁶ There were no indications that the supervised sessions in the Nielsen trial were less stringent compared with the later studies.¹⁸

Reported data of walking time and distance were standardized to be able to calculate the difference in increase between the two treatment groups. Translating the standardized data back to walking distances, the summary estimates of the maximal treadmill walking distance showed approximately 150 meters difference in increase in favour of the supervised exercise therapy regimens over the non-supervised therapy after three months of therapy. This difference was maintained at six months. In order to determine the clinical relevance of the ability to walk 150 meters further, one should realize that a mean maximal walking distance at baseline is approximately 300 meters with an even shorter pain-free walking distance of approximately 200

meters. Hence, these mostly elderly patients with symptomatic PAD become more independent. However, differences in quality of life in the four out of seven trials that measured this patient-reported outcome were not striking.

There are several plausible mechanisms that might explain the beneficial results of supervised exercise therapy over non-supervised regimens. A first explanation could be the fact that the exercise regimen of the supervised exercise therapy group mainly consisted of treadmill walking, which has a higher workload than level ground walking at 'normal' speed used by the non-supervised group.²³ It is very difficult to measure the intensity of training, but it is generally assumed that home training cannot be considered to be performed with the same energy as training under supervision.¹⁸ Secondly, a higher workload will lead to a larger positive effect of the general physical condition of the patient, possibly due to an increased cardiovascular stress, providing a better stimulus for exercise-induced adaptations. A small study was able to show a relationship between the general physical condition and walking distance in the current population by using upper-limb exercise to increase the maximal walking distance.²⁴ Furthermore, a supervised program could offer additional encouragement and motivation to the patients with a higher adherence rate. Nevertheless, taking compliance into account, from the contrasting results between the two trials^{16,23}, nothing can be suggested about the influence of a supervised exercise regimen on the compliance. However, compliance in a supervised exercise setting is effortlessly measurable during the session in contrast to compliance during the home-based intervals or the home-based settings.

Due to the inclusion criteria used in the trials for example, age restrictions and diagnosis based on a clinical history, and exclusion criteria such as the presence of diabetes mellitus and smoking behaviour, generalization of the results of this meta-analysis could be a topic of discussion. Unfortunately, the raw data of one study were not directly available and had to be derived by working backwards from the reported P values.¹⁶ We assumed that the standard deviations of both groups were equal. Compared with the other two large trials^{19,20}, that reported equal standard deviations, this seemed reasonable.

Regular exercise, such as walking, has been shown to reduce significantly cardiovascular events.^{25,26} Since claudicants have a high cardiovascular morbidity and mortality (30% mortality at five years)²⁷⁻²⁹, a habit of regular walking could be of considerable importance. However, there are no data to substantiate the results of regular walking on mortality in these patients.

Authors' conclusions

Implications for practice

Supervised exercise therapy has statistically significant benefits on treadmill walking distance compared with non-supervised regimens, which is currently the main prescribed exercise therapy for people with intermittent claudication. The clinical relevance of this difference will require additional studies with a focus on the improvements in quality of life.

This review suggests that supervised exercise therapy programs should be available in the care of medically fit people with intermittent claudication.

Implications for research

A supervised rehabilitation program of treadmill walking had significantly greater efficacy than a non-supervised program for improving walking ability in people with intermittent claudication. Ideally, these effects should be demonstrated to be maintained long term and to translate into effects on long term morbidity and mortality.

A supervised exercise program results in optimal walking improvement and should be compared with other interventions (angioplasty, surgery, with or without the combination of exercise therapy) for both walking and quality of life improvement.

Table 1: Exercise therapy regimen

Trial	Mode of exercise	End point used during ET	Duration of ET minutes	Length of ET program weeks	Frequency of exercise per week	Treadmill test Speed, km/h (grade, %)	Additional motivation
Nielsen ¹⁸	Combination, walking dominating	Maximal intensity	60	12	3	3.84 (8)	--
Nielsen ¹⁹	Walking	--	60	12 SV + 40 NS; 52 NS	3	5 (8)	--
Patterson ²⁰	Combination (cardio-vascular)	70% of maximal (SV); Tolerance (NS)	60 (SV); 20 increasing to 40 (NS)	12	3	1.6 (5) increasing up to 4 (10)	Lectures weekly. Phone call if absent (SV); 1.5 h/w direct contact (NS)
Regensteiner ²¹	Walking	Moderate pain	35 increasing to 55	12	3	3.2 (0-.. +3.5 / 3 min)	Phone contact weekly (NS)
Savage ²²	Walking	Intense pain	15 increasing to 40	12 SV + 12 NS (SV); 24 NS	3	3.2 (0-.. +2 / 2 min)	Phone contact monthly (NS)
Degischer ²³	Walking	60% of maximal	60	12	3 (SV) 7 (NS)	3.2 (0-.. +2 / 2 min)	4 patients at once (SV); Education at baseline (NS)
Cheetham ¹⁶	Combination	Near maximal	30	24	1 (SV) 3 (NS)	3.5 (12)	10 min talk (SV) 14 patients at once (SV)
Kakkos ¹⁷	Walking	Moderate pain (SV) Near maximal pain (NS)	60 (SV) ≥45 (NS)	24	3	3.5 (10)	--

ET=exercise therapy; SV=supervised exercise therapy group; NS=non-supervised exercise therapy group

Table 2: Effect estimates maximal treadmill walking distance

Outcome	Trial	Reported value Mean (SD)		Standardised value Mean (SD)		Effect Estimate
		Supervised ET	Non-supervised ET	Supervised ET	Non-supervised ET	Effect (95% CI)
3 months	Nielsen ¹⁸	2.3 min (1.4 min)	2.9 min (1.6 min)	n=25 0.88 (0.54)	n=26 1.11 (0.61)	-0.39 [-0.95, 0.16]
	Patterson ²⁰	9.9 min (4.9 min)	8.5 min (4.9 min)	n=25 1.17 (0.47)	n=23 0.82 (0.47)	0.73 [0.15, 1.32]
	Regensteiner ²¹	10.9 min (4.5 min)	6.5 min (4.2 min)	n=10 1.25 (0.52)	n=10 0.75 (0.48)	0.96 [0.02, 1.89]
	Savage ²²	833.3 m (376.3 m)	736.5 m (290.3 m)	n=11 1.06 (0.48)	n=10 0.94 (0.37)	0.27 [-0.59, 1.13]
	Degischer ²³	905.6 m (439.8 m)	588.5 m (212.9 m)	n=19 1.23 (0.60)	n=21 0.80 (0.29)	0.91 [0.25, 1.56]
	Cheetham ¹⁶	220.0 m (80.9 m)	119.0 m (80.9 m)	n=28 1.30 (0.48)	n=28 0.71 (0.48)	1.21 [0.64, 1.79]
						Overall effect: 0.58 [0.31, 0.85] P<0.0001
6 months	Patterson ²⁰	14.6 min (6.1 min)	8.5 min (3.1 min)	n=19 1.26 (0.53)	n=19 0.74 (0.27)	1.21 [0.51, 1.91]
	Savage ²²	741.9 m (365.6 m)	715.0 m (394.4 m)	n=11 1.02 (0.50)	n=10 0.98 (0.54)	0.07 [-0.78, 0.93]
	Degischer ²³	846.0 m (397.2 m)	551.6 m (241.9 m)	n=19 1.22 (0.57)	n=21 0.80 (0.35)	0.88 [0.23, 1.53]
	Cheetham ¹⁶	302.0 m (102.4 m)	174.0 m (102.4 m)	n=28 1.27 (0.43)	n=28 0.73 (0.43)	1.24 [0.66, 1.81]
	Kakkos ¹⁷	220.0 m (282.5 m)	140.0 m (60 m)	n=8 1.24 (1.59)	n=9 0.79 (0.34)	0.38 [-0.58, 1.35]
						Overall effect: 0.89 [0.57, 1.21] P<0.0001
9 months	Cheetham ¹⁶	305.0 m (112.8 m)	164.0 m (112.8 m)	n=28 1.30 (0.48)	n=28 0.70 (0.48)	1.23 [0.66, 1.81] P<0.0001
12 months	Cheetham ¹⁶	304.0 m (104.0 m)	175.0 m (104.0 m)	n=27 1.28 (0.44)	n=28 0.73 (0.44)	1.23 [0.65, 1.81]
	Kakkos ¹⁷	270.0 m (700.0 m)	135.0 m (57.5 m)	n=6 1.40 (3.63)	n=8 0.70 (0.30)	0.28 [-0.79, 1.34]
						Overall effect: 1.01 [0.50, 1.52] P<0.0001

SD: standard deviation; ET: exercise therapy; CI: confidence interval

Table 3: Effect estimates pain free treadmill walking distance

Outcome	Trial	Reported value		Standardised value		Effect Estimate
		Supervised ET	Non-supervised ET	Supervised ET	Non-supervised ET	
3 months	Nielsen ¹⁸	269.0 m (121.0 m)	271.0 m (114.0 m)	n=26 1.00 (0.45)	n=26 1.00 (0.42)	0.00 [-0.54, 0.54]
	Patterson ²⁰	10.8 min (5.6 min)	6.1 min (4.0 min)	n=25 1.26 (0.66)	n=23 0.71 (0.47)	0.94 [0.34, 1.54]
	Regensteiner ²¹	5.0 min (3.4 min)	2.9 min (1.4 min)	n=10 1.27 (0.86)	n=10 0.73 (0.35)	0.79 [-0.13, 1.71]
	Savage ²²	456.9 m (317.2 m)	225.8 m (150.5 m)	n=11 1.32 (0.91)	n=10 0.65 (0.43)	0.89 [-0.02, 1.80]
	Degischer ²³	495.9 m (361.6 m)	255.6 m (134.3 m)	n=19 1.34 (0.98)	n=21 0.69 (0.39)	0.87 [0.22, 1.52]
	Overall effect: 0.61 [0.31, 0.91] p<0.0001					
6 months	Patterson ²⁰	11.3 min (4.0 min)	6.6 min (3.3 min)	n=19 1.26 (0.45)	n=19 0.74 (0.37)	1.24 [0.54, 1.94]
	Savage ²²	483.8 m (317.2 m)	263.4 m (155.9 m)	n=11 1.28 (0.84)	n=10 0.70 (0.41)	0.83 [-0.07, 1.73]
	Degischer ²³	461.9 m (280.4 m)	270.1 m (140.5 m)	n=19 1.28 (0.78)	n=21 0.75 (0.39)	0.86 [0.20, 1.51]
	Kakkos ¹⁷	70.0 m (45.0 m)	70.0 m (35.0 m)	n=8 1.00 (0.64)	n=9 1.00 (0.50)	0.00 [-0.95, 0.95]
	Overall effect: 0.83 [0.44, 1.21] p<0.0001					
12 months	Nielsen ¹⁸	247 m (142 m)	234 m (152 m)	n=26 1.03 (0.59)	n=26 0.97 (0.63)	0.10 [-0.45, 0.64]
	Kakkos ¹⁷	90.0 m (50.0 m)	80.0 m (55.0 m)	n=6 1.07 (0.59)	n=8 0.95 (0.65)	0.18 [-0.88, 1.24]
	Overall effect: 0.11 [-0.37, 0.60] p=0.64					

SD: standard deviation; ET: exercise therapy; CI: confidence interval

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8

Supervised exercise therapy for intermittent claudication in a community-based setting

Chapter 10: Vascular and Endovascular Challenges – Community and

BLW Bendermacher

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Summary box

- **Supervised exercise therapy programs have significant benefits compared with non-supervised programs.**
- **Community-based supervised exercise therapy has both economic and logistic advantages over clinic-based supervised exercise therapy.**
- **Community-based supervised exercise therapy programs seems to be as effective as supervised exercise therapy provided in a clinic-based setting and is a promising approach to providing conservative treatment for patients with intermittent claudication.**
- **Supervised exercise therapy in a community-based setting should ideally be the initial standard of care for patients with intermittent claudication, however, a study of the cost-effectiveness should be awaited.**

Introduction

The primary and most effective treatment for patients with intermittent claudication is exercise therapy.¹ An overall improvement in maximal walking ability of approximately 150% was described, whereas significant improvements in walking time were shown comparing exercise with angioplasty or antiplatelet therapy.²

In regular care, exercise therapy is usually prescribed in the form of advice to “go home and walk”, without supervision or follow-up.^{3,4} Yet, there is no evidence to support the efficacy of this advice and compliance is known to be low.^{3,5} Factors, such as fear of pain, inadequate knowledge and poor general condition, contribute to the difficulty of starting, sustaining and maintaining exercise therapy.³

Supervised exercise therapy entails adequate coaching to increase the maximal walking distance as well as coaching in the necessary changes in life-style, such as smoking cessation, weight control, and increase in overall exercise. Unfortunately, supervised programs are sporadically available.⁶ The supervised programs as described in literature so far were provided in a clinic-based setting. However, in our hospital we experienced that supervised exercise therapy in a clinic-based setting has several disadvantages:

1. Limited capacity: three half-hour sessions weekly per patient proved overly time consuming for an already busy department of physiotherapy and rehabilitation. Consequently, only a limited number of patients can be offered clinic-based supervised exercise therapy.
2. High transport costs: transport to and from the hospital, especially using public transportation, is costly for many patients.
3. Time consuming: the need to visit the hospital two to three times weekly in the initial phase can be problematic for a majority of patients, especially for the patients who do not live nearby the hospital.

In this chapter, supervised exercise therapy will be compared with non-supervised exercise therapy programs and the superiority of supervised exercise therapy will be demonstrated. Based on this knowledge as well as our experience with clinic-based supervised exercise therapy, a new community-based concept of supervised exercise therapy was developed and implemented. This development and implementation will be addressed. Furthermore, the first results of the community-based supervised exercise therapy program will be presented and compared with the results of supervised exercise therapy programs provided in clinical settings, as described in literature.

Supervised exercise therapy versus non-supervised exercise therapy

Eight clinical trials compared supervised exercise therapy with non-supervised exercise therapy, all involving a small number of patients (range 20–59).^{5,7–13} A meta-analysis of their data on walking distance consistently demonstrated statistically significant and clinically relevant differences in improvement of walking distances in favour of supervised exercise therapy.¹⁴

Reported data of walking time and distance were standardized to be able to calculate the difference in increase between the two treatment groups. Translating the standardized data back to walking distances, the summary estimates of the maximal treadmill walking distance showed approximately 150 meters difference in increase in favour of the supervised exercise therapy regimens over the non-supervised therapy after three months of therapy. This difference was maintained at six months (Table I).

In order to determine the clinical relevance of the ability to walk 150 meters further, one should realise that a mean maximal walking distance at baseline is approximately 300 meters with an even shorter pain-free walking distance of approximately 200 meters. Hence, these mostly elderly patients with symptomatic peripheral arterial disease (PAD) become more independent after increasing their walking distance. However, differences in quality of life, measured in four out of eight trials were not striking.

There are several plausible mechanisms that might explain the beneficial results of supervised exercise therapy over non-supervised regimens. A first explanation could be the fact that the exercise regimen of the supervised exercise therapy group mainly consisted of treadmill walking, which has a higher workload than level ground walking at 'normal' speed used by the non-supervised group.⁸ It is difficult to measure the intensity of training, but it is generally assumed that home training cannot be considered to be performed with the same energy as training under supervision.¹⁰ Secondly, a higher workload will lead to a larger positive effect on the general physical condition of the patient, possibly due to an increased cardiovascular stress, providing a better stimulus for exercise-induced adaptations. A small study was able to show a relation between the general physical condition and walking distance in the current population by using upper-limb exercise to increase the maximal walking distance.¹⁵ Furthermore, a supervised program could offer additional encouragement and motivation to the patients with a higher adherence rate. Nevertheless, taking compliance into account, from the contrasting results between the two trials^{7,8}, nothing can be suggested about the influence of a supervised exercise regimen on compliance. However, compliance in a supervised exercise setting is effortlessly measurable during the session in contrast to compliance during the home-based intervals or the home-based settings. A possible solution to the difficulties in measuring compliance during home-based exercise is a Personal Activity Monitor (PAM). Patients should wear this small device all day, and by means of a storage function the amount of activity can be measured. The usefulness of a PAM in patients with intermittent claudication in enlarging compliance is currently being determined.

Supervised exercise therapy provided in a community-based setting

Based on the knowledge that supervised exercise therapy is more effective than non-supervised exercise therapy, as well as the mentioned disadvantages of supervised exercise therapy in a clinic-based setting, a new community-based concept of supervised exercise therapy was developed and implemented; the so called Network for Exercise Therapy, Parkstad (NETP).¹⁶ We hypothesized that the community-based concept of well distributed physiotherapeutic practices offers supervised exercise therapy closer to patients' homes and consequently lowers transport costs and time.

Development and implementation of the Network for Exercise Therapy, Parkstad

In October 2003, all 59 regional physiotherapy practices (over 100 physiotherapists) were invited to attend a mini-symposium regarding supervised exercise therapy in a physiotherapeutic setting. Physiotherapists interested in providing exercise therapy were asked to register and five physiotherapists were invited to join a steering committee. Within the steering committee four task groups were formed:

1. Exercise therapy education
2. Exercise therapy implementation
3. Inter-professional communication
4. Exercise therapy prolongation

In June 2004 an accredited two-day in hospital educational program on supervised exercise therapy was provided by the Royal Dutch Society for Physiotherapy and the Dutch Paramedic Institute. Twenty-nine practices were selected, equally dispersed over the southeaster part of Limburg as well as the department of physiotherapy and rehabilitation in our hospital (Figure II). Together, 30 practices are participating in the NETP, by number addressing the previously mentioned capacity problem of clinic-based supervised exercise therapy.

To facilitate inter-professional communication as well as for research purposes a web-based database was developed. Since supervised exercise therapy is only reimbursed for a period of one year, three walking groups were installed (once a week each) based on volunteers (former NETP patients) as well as physiotherapy students from the Hogeschool Zuyd (Physiotherapy academy) in Heerlen as coaches. After one year of supervised exercise therapy (or even during that year) patients can join the nearest by walking group for a once a week training session. Besides, smoking at these sessions is strictly prohibited.

After implementation of the NETP, patients with PAD who are eligible for supervised exercise therapy are referred to a nearby physiotherapist participating in the network. During a period of one year, approximately 30 physiotherapeutic sessions per patient take place. Reimbursement from the tenth session through the remainder of the 12 months is financed by National Insurance of Health Care (AWBZ). Reimbursement for the initial nine sessions depends on the patient's insurance policy.

Supervised exercise therapy program

Supervised exercise therapy is administered according to the guidelines of the Royal Dutch Society for Physiotherapy.¹⁷ The mode of exercise is mainly treadmill walking up to maximal pain, alternated with other cardiovascular training and strength training. During the training sessions, walking patterns were corrected to ameliorate the quality of walking. In general, patients received two to three sessions a week of approximately 30 minutes each in the initial phase, phasing down to once every two weeks and then to once every month. Additionally, patients were encouraged to exercise daily by walking as much as possible to near-maximal pain.

To evaluate supervised exercise therapy in time, walking distances were measured by a progressive treadmill exercise test with a constant walking speed of 3.2 km/h beginning at 0% incline with an increasing grade of 2% every 2 minutes. The outcomes for walking distance are the initial and absolute claudication distance (ICD and ACD, respectively). ICD was defined as the moment at which the patient preferred to stop because of pain when no supervision was provided. ACD was defined as the maximal possible walking distance.

*First results of a community-based supervised exercise therapy program:**Network for Exercise Therapy, Parkstad*

From January to October 2005, 93 consecutive patients with intermittent claudication were eligible for community-based supervised exercise therapy and included in the study cohort. During the 6-months study period, 37 patients (39.8%) discontinued the program (Figure 1). Of these 37, 10 experienced insufficient symptom relieve and eventually underwent a vascular intervention. Three patients quit the program at 3, 4, and 5 months of supervised exercise therapy, respectively, stating that they were satisfied with the regained walking distance and did not require further supervised exercise therapy. Ten patients were not motivated sufficiently to continue the program and none of these sought medical attention for intermittent claudication elsewhere. In three patients, a lack of adequate insurance coverage was the reason for dropping out. A total of eleven patients quit the program because of emerging disease (cardiovascular (n=6), pulmonary (n=1), orthopaedic (n=2), renal insufficiency (n=1)), or death (n=1, ruptured abdominal aortic aneurysm).

Data for the remaining 56 patients were used to analyze the change in walking distance over the 6-month study period. The baseline characteristics are shown in Table II. Of the 56 patients, two (3.6%) had severe chronic heart failure. Based on this cardiac co-morbidity, both patients were referred for supervised exercise therapy to the department of physiotherapy and rehabilitation in our hospital instead of a community-based physiotherapist.

Walking distances

At baseline, the mean ICD was 395 m (range: 55–1600 m) with a mean ACD of 563 m (range: 60–1700 m). After 3 months of supervised exercise therapy these values significantly improved to a mean ICD of 840 m (range: 180–2260 m) and a mean ACD of 1154 m (range: 290–3740 m). The means for both distances further increased after 6 months, with a mean ICD of 1005 m (range: 210–3810) and a mean ACD of 1312 m (range: 270–3980 m). Translating these results to percentage increases, ICD increased 187% and ACD increased 142% after 3 months. After 6 months ICD increased 240% and ACD 191% (Table III).

Community-based versus clinic-based supervised exercise therapy

There are earlier studies reporting ACD results after supervised exercise therapy compared to non-supervised exercise therapy in patients with intermittent claudication^{5,7-10,12,13}; however, in these studies supervised exercise therapy was provided in a clinic-based setting and sample sizes were small (range: 8–28 subjects). To compare these results with those of our community-based supervised exercise therapy results, we summarized the reported ACD or absolute claudication time (ACT) of the clinic-based supervised exercise therapy groups for each follow-up time point. For each trial, the percentage increase in ACD or ACT was calculated as shown in Table IV. After 3 months of clinic-based supervised exercise therapy, increases between 35% and 137% were found, with a mean increase of 76%, compared with a mean increase of 142% in a community-based setting. After 6 months, an increase of 90% occurred (range: 42%–159%) in a clinic based setting, compared to 191% in a community-based supervised exercise therapy.

Discussion

Community-based supervised exercise therapy

Supervised exercise therapy provided in a patient's home neighbourhood, in a so-called community-based physiotherapeutic setting, resulted in a highly statistically significant improvement in ACD after 3 and 6 months. Although a comparison of these favourable results with historical studies should be regarded with caution because of the variability in the prescribed exercise regimens and treadmill walking tests used, supervised exercise therapy in a community-based setting seems to be at least as efficacious as the programs provided in a clinical setting.

Because we studied consecutive patients who were routinely referred to the new community-based supervised exercise program, we were able to document carefully the reasons for program discontinuation, as can also be done in routine clinical practice. In our case, 37 patients (39.8%) who were referred to the community-based supervised exercise therapy did not continue the program for a full 6-months period. Approximately a quarter of these patients stopped because of intercurrent diseases, while in another quarter the supervised exercise therapy did not lead to adequate improvement and the patients had to undergo a vascular intervention. Overall, our

recorded withdrawal rate seems to be comparable to those of trials studying supervised exercise therapy in a clinic-based setting, which reported drop-out rates up to 43%.^{5,7,9}

One of the possible pitfalls of community-based supervised exercise therapy is the use of numerous physiotherapeutic practices (30) and physiotherapists (41), which results in a lower patient volume for each physiotherapist than occurs in a clinic-based setting. For this reason, we decided to implement a NETP and refer patients only to physiotherapists who participate in this network, instead of to any physiotherapist. Regular training sessions with all participating physiotherapists in the NETP ensures shared knowledge and experience. In addition, community-based supervised exercise therapy creates a larger capacity compared to clinic-based supervised exercise therapy, which means that a greater number of patients with intermittent claudication can be treated.

Treadmill tests

The treadmill tests used to measure the walking distances vary widely in all reported studies. Overall, two contrasting treadmill protocols have been used to measure walking distances in patients with intermittent claudication. First, a constant load test, with both a constant speed as well as a constant grade has been developed.¹⁸⁻²⁰ However it should be noted that within specific protocols and studies, the speed varies between 2.4 and 3.2 km/h and a 0% – 12% incline. Although this test is easy to administer, the variance coefficient is between 30% and 40%.^{19,21} Consequently, repeated measurements are needed for a sufficient assessment of the walking distance. On the other hand, patients with a highly compromised circulation may be difficult to test at high initial workloads.²²

A progressive treadmill test starts with a low initial workload that progressively increases until claudication pain forces cessation of exercise.^{20,23-25} This low initial work load is achieved by a constant speed and increasing grade. In comparison of the constant treadmill test with the progressive test, test process-related variances showed a comparable magnitude for both tests and were independent of the claudication distance ranges.²² However, for a subgroup of patients with a maximal walking distance of 100 meters or less, measured by a constant treadmill test (3.2 km/h, 12% incline), the workload of that test is suggested to be too high to allow for an appropriate separation of different claudication distances, resulting in a substantial drop in the between-subject variance for the constant treadmill test.²²

Because the initial workload of the graded test is low, this problem can be avoided and even patients with severe PAD can be tested with reasonable accuracy. For this reason, in the current study a progressive treadmill test instead of a constant load treadmill test was used for evaluation of the walking distances after supervised exercise therapy.

Future perspectives

At this moment a multicenter prospective randomized trial is being performed to determine the cost-effectiveness of community-based supervised exercise therapy, with or without therapy feedback (PAM), in comparison with non-supervised exercise therapy. Supervised exercise therapy has proven to be more effective than non-supervised exercise therapy, however, with a uncertain cost-effectiveness. The provided therapy feedback by the PAM might increase the intensity of supervised exercise therapy and might lead to a reduction in the duration and number of physiotherapeutic sessions. Results are expected in 2008.

Another question that needs to be addressed, is the effect of supervised exercise therapy on patients with recurrent complaints of intermittent claudication and a history of a previous vascular intervention. It is known that lower-extremity revascularisation procedures in patients with PAD have a substantial failure rate over time.²⁶ Complaints of intermittent claudication may reoccur. The effectiveness of supervised exercise therapy in this specific population needs to be determined.

Likewise, little is known about the effect of supervised exercise therapy direct following a vascular intervention for PAD. Many patients keep or regain symptoms of intermittent claudication after a vascular intervention, despite the fact that the treated segment is patent.²⁷⁻³⁰ At this point the possible value of supervised exercise therapy should be explored.

Conclusion

Supervised exercise therapy has significant benefits on treadmill walking distance compared with non-supervised regimens. However, non-supervised exercise therapy is currently the main prescribed exercise therapy for people with intermittent claudication. Supervised exercise therapy for patients with intermittent claudication in a community-based setting, seems as effective as supervised exercise therapy provided in a clinical setting.

Table 1: Effect estimates maximal treadmill walking distance

Outcome	Trial	Reported value Mean (SD)		Effect Estimate
		Supervised ET	Non-supervised ET	Effect (95% CI)
3 months	Nielsen ¹⁰	n=25 2.3 min (1.4 min)	n=26 2.9 min (1.6 min)	-0.39 [-0.95, 0.16]
	Patterson ⁵	n=25 9.9 min (4.9 min)	n=23 8.5 min (4.9 min)	0.73 [0.15, 1.32]
	Regensteinen ²	n=10 10.9 min (4.5 min)	n=10 6.5 min (4.2 min)	0.96 [0.02, 1.89]
	Savage ¹³	n=11 833.3 m (376.3 m)	n=10 736.5 m (290.3 m)	0.27 [-0.59, 1.13]
	Degischer ⁸	n=19 905.6 m (439.8 m)	n=21 588.5 m (212.9 m)	0.91 [0.25, 1.56]
	Cheetham ⁷	n=28 220.0 m (80.9 m)	n=28 119.0 m (80.9 m)	1.21 [0.64, 1.79]
		Overall effect: 0.58 [0.31, 0.85] (p<0.0001) ≈150 meters difference in increase		
6 months	Patterson ⁵	n=19 14.6 min (6.1 min)	n=19 8.5 min (3.1 min)	1.21 [0.51, 1.91]
	Savage ¹³	n=11 741.9 m (365.6 m)	n=10 715.0 m (394.4 m)	0.07 [-0.78, 0.93]
	Degischer ⁸	n=19 846.0 m (397.2 m)	n=21 551.6 m (241.9 m)	0.88 [0.23, 1.53]
	Cheetham ⁷	n=28 302.0 m (102.4 m)	n=28 174.0 m (102.4 m)	1.24 [0.66, 1.81]
	Kakkos ⁹	n=8 220.0 m (282.5 m)	n=9 140.0 m (60 m)	0.38 [-0.58, 1.35]
		Overall effect: 0.89 [0.57, 1.21] (p<0.0001) ≈225 meters difference in increase		

SD: standard deviation; ET: exercise therapy; CI: confidence interval

Table II: Demographic and clinical characteristics of patients referred for community-based supervised exercise therapy

	Analysed population (n=56)	Drop-outs (n=37)
Age (y), mean (SD)	64.0 (10.4)	64.7 (10.8)
Men, n (%)	35 (62.5)	25 (67.6)
BMI, mean (SD)	26.3 (3.9)	26.1 (3.9)
Current smokers, n (%)	24 (42.9)	11 (29.7)
Ever smoked, n (%)	19 (33.9)	13 (35.1)
Never smoked, n (%)	13 (23.2)	10 (27.0)
Hypertension, n (%)	45 (80.4)	31 (83.8)
Diabetes mellitus, n (%)	23 (41.1)	13 (35.1)
Hypercholesterolemia, n (%)	49 (87.5)	26 (70.3)
Coronary heart disease, n (%)	16 (28.6)	9 (24.3)
Stroke or TIA, n (%)	4 (7.1)	9 (24.3)
COPD, n (%)	9 (16.1)	4 (10.8)
ABI, mean (SD)	0.73 (0.18)	0.70 (0.14)

SD: standard deviation; BMI: body mass index; TIA: transient ischemic attack; COPD: chronic obstructive pulmonary disease; ABI: ankle brachial index

Table III: Mean percentage increase in walking distances of patients referred for community-based supervised exercise therapy (n=56)

Follow-up	ICD		ACD	
	Mean % (SD)	Range (%)	Mean % (SD)	Range (%)
1 month	80.9 (402.0) p<0.0001	-53.9 - 579.0	73.8 (105.5) p<0.0001	-32.1 - 515.4
3 months	187.3 (187.1) p<0.0001	-25.5 - 772.7	142.2(150.0) p<0.0001	-24.8 - 728.3
6 months	240.2 (284.2) p<0.0001	-39.8 - 1282.5	190.6 (229.5) p<0.0001	-22.9 - 1187.6

ICD: intial claudication distance; ACD: absolute claudication distance; SD: standard deviation

Table IV: Increase in ACD in prior studies using supervised exercise therapy in primary claudicants

Trial	Number of patients	Duration of supervised ET therapy (months)	Increase in acd (%)	
			3 months	6 months
Cheetham ⁷	28	6	66.6	128.8
Degischer ⁸	19	3	82.4	70.4
Kakkos ⁹	8	6	--	51.7
Savage ¹³	11	6	59.8	42.3
Nielsen ¹⁰	25	3	35.3	--
Patterson ⁵	25	3	75.5	158.9
Regensteiner ¹²	10	3	137.0	--
Mean % increase overall			76.1	90.4

ACD: absolute claudication distance

Figure 1: Flowchart of analyzed population

Figure II: Map of the Network of Exercise Therapy, Parkstad

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**Supervised exercise therapy for intermittent claudication
in a community-based setting is as effective as clinic-based**
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Abstract

Introduction: Supervised exercise therapy for intermittent claudication, provided in a clinical setting, has shown to be superior compared to non-supervised exercise therapy. To offer patients with intermittent claudication the possibility of a one year supervised exercise therapy program close to their home, a regional network of physiotherapists was developed and implemented. The aim of this study was to determine the effect of supervised exercise therapy provided in a community-based setting on walking distances.

Methods: The cohort study included all consecutive patients presenting at the vascular outpatient clinic with intermittent claudication, diagnosed by a resting ankle brachial index below 0.9, who had no previous peripheral vascular intervention for peripheral arterial disease, no major amputation, and sufficient command of the Dutch language. The exclusion criterion was the inability to walk the baseline treadmill test for a minimum of 10 meters. The examined intervention was supervised exercise therapy in a community-based setting. A progressive treadmill test at baseline and at 1, 3, and 6 months of follow-up measured initial claudication distance and absolute claudication distance. Changes were calculated using the mean percentages of change.

Results: From January through October 2005, 93 consecutive claudicants were eligible. Overall, 37 patients discontinued the supervised exercise therapy program.

Eleven of these patients stopped because of intercurrent diseases, while for 10 supervised exercise therapy did not lead to adequate improvement and underwent a vascular intervention. Three patients quit the program stating that they were satisfied with the regained walking distance and did not require further supervised exercise therapy. Ten patients were not motivated sufficiently to continue the program, and in three patients, a lack of adequate insurance coverage was the reason for dropping out.

Data for 56 patients were used, showing a mean percentage increase in initial claudication distance of 187% and 240% after 3 and 6 months, respectively. Mean percentage of the absolute claudication distance increased 142% and 191% after 3 and 6 months, respectively.

Conclusion: Supervised exercise therapy in a community-based setting is a promising approach to providing conservative treatment for patients with intermittent claudication.

Introduction

Exercise therapy is highly efficacious for symptomatic relief in peripheral arterial disease (PAD)¹, but is usually prescribed simply in the form of advice to “go home and walk”, without supervision or follow-up.^{2,3} Yet, there is no evidence to support the efficacy of this advice, and compliance is known to be low.^{2,4} A recent Cochrane review identified a significant improvement in walking distance in patients undergoing a supervised exercise therapy program compared with those involved in a non-supervised program, with an increased difference in maximal walking distance of approximately 150 meters after 3 months.⁵ Factors, such as fear of pain, inadequate knowledge of the underlying disease, and poor general condition, contribute to the difficulty of starting, sustaining, and maintaining exercise therapy.² Supervised exercise therapy entails adequate coaching to increase the maximal walking distance as well as coaching in the necessary changes in life-style, such as smoking cessation, weight control, and increase in overall exercise.

Based on this difference with supervised exercise therapy, we explored its local implementation in a clinic-based setting; however, we had to stop the study for the following reasons. A major restriction appeared to be the limited capacity of the in-hospital department of rehabilitation and physiotherapy. Three half-hour sessions weekly per patient proved overly time consuming in an already busy department. Consequently, only a limited number of patients could be offered clinic-based supervised exercise therapy. Furthermore, transport to and from the hospital, especially using public transportation, was costly for many patients, as well as time consuming. The initial phase of two to three sessions weekly especially appeared to be problematic for a majority of patients. Some of them were too tired upon arriving at the hospital to start training at all. Recorded drop-out rates of up to 43% in the literature convinced us not to pursue further clinic-based supervised exercise therapy.⁶⁻⁸

Based on this experience, a new community-based concept of supervised exercise therapy was developed and implemented, resulting in the so-called Network for Exercise Therapy, Parkstad (NETP).⁹ In this study we hypothesized that the community-based concept of well-distributed physiotherapeutic practices offers supervised exercise therapy closer to patients' homes and consequently lowers transport costs and time. The NETP consists of 29 physiotherapeutic practices equally dispersed over the southeastern part of Limburg, as well as the department of rehabilitation and physiotherapy in our hospital. By using 30 practices, we also addressed the capacity problem.

Patients and methods

Study population

After implementation of the NETP, patients with PAD who were eligible for supervised exercise therapy were referred to a nearby physiotherapist participating in the network. All consecutive patients with intermittent claudication, diagnosed at the vascular

laboratory by a resting ankle brachial index (ABI) below 0.9, who had no previous vascular intervention for PAD, no major amputation (below knee or more proximal), and sufficient command of the Dutch language, were considered for community-based supervised exercise therapy. Patients were excluded from the analyses when the absolute claudication distance (ACD) at baseline was 10 meters or less.

All patients received a platelet inhibitor and a statin as recommended in the Dutch guidelines for PAD from the Dutch Association of Surgery within the scope of secondary prevention in patients with PAD.¹⁰ Patients were included from January to October 2005.

Measurements

At baseline, the ABI was measured at the vascular laboratory¹¹, and vascular risk factors (smoking, diabetes, hypertension, hypercholesterolemia, myocardial infarction, angina pectoris, and stroke) were registered by the vascular surgery nurse practitioner. For smoking, patients were categorized as current smokers, former smokers, and patients who never smoked. Diabetes was noted with a serum fasting glucose level ≥ 6.0 mmol/L and/or if glucose lowering medication was prescribed. Hypertension was noted for a blood pressure reading of $\geq 140/90$ mmHg, and/or the use of antihypertensive medication, and hypercholesterolemia was defined as a serum total cholesterol of ≥ 5.0 mmol/L or the use of cholesterol-lowering medication.

Walking distances were measured by a progressive treadmill exercise test with a constant walking speed of 3.2 km/h beginning at 0% incline and increasing grade by 2% every 2 minutes.¹² The outcomes for walking distance were the initial claudication distance (ICD) and absolute claudication distance (ACD). ICD was defined as the moment at which the patient preferred to stop because of pain when no supervision was provided. ACD was defined as the maximal possible walking distance. ICD and ACD measurements were taken at baseline and at 1, 3, and 6 months.

Exercise program

Supervised exercise therapy was administered according to the guidelines of the Royal Dutch Society for Physiotherapy.¹³ The mode of exercise was mainly treadmill walking up to maximal pain. Treadmill training was alternated with cardiovascular training and strength training. During the training sessions, walking patterns were corrected to improve the quality of walking. In general, patients received two to three sessions a week of approximately 30 minutes each in the initial phase, phasing down to once every two weeks. Additionally, patients were encouraged to exercise daily by walking as much as possible to near-maximal pain.

Reimbursement from the tenth session through the remainder of the 12 months is financed by National Insurance of Health Care (AWBZ). Reimbursement for the initial nine sessions depends on the patient's insurance policy.

Statistical analyses

The effects of community-based supervised exercise therapy on ICD and ACD were measured as outcome measurements. These were expressed as the percentage increase in walking distance compared to baseline. For each patient, the increase in ACD and ICD was calculated. The statistical significance of the increases was compared using the paired Students' t-test. If a decision was made to perform a vascular intervention during the supervised exercise therapy period, the patient was excluded from further analyses. A p-value of 0.05 or less was considered to be statistically significant. Statistical analyses were performed using SPSS 11.0.

We lacked a clinic-based supervised exercise therapy control group because of the above mentioned limiting factors; thus, we compared the increase in ICD and ACD of community-based supervised exercise therapy participants and drop-out rates with published data for clinic-based supervised exercise therapy from the Cochrane review.⁵ Because five out of a total of seven studies in this review were limited to six-month follow-up periods, we present and compare the results of 6 months of community-based supervised exercise therapy.

Results

From January to October 2005, 93 consecutive patients with intermittent claudication were eligible for community-based supervised exercise therapy and included in the study cohort. During the 6-month study period, 37 patients (39.8%) discontinued the program. Of these 37, 10 experienced insufficient symptom relief and eventually underwent a vascular intervention. Of these 10 patients, 6 received a percutaneous transluminal angioplasty (PTA) in one or both iliac arteries, 3 received a PTA in the femoral artery, and one aortobifemoral bypass was performed. All of these 10 patients were unsatisfied with their claudication complaints. Three patients quit the program at 3, 4, and 5 months of supervised exercise therapy, respectively, stating that they were satisfied with the regained walking distance and did not require further supervised exercise therapy. Their three-months results showed an increase between 110 and 170% increase in ACD. Ten patients were not motivated sufficiently to continue the program, and none of these sought medical attention for intermittent claudication elsewhere. In three patients, a lack of adequate insurance coverage was the reason for dropping out. A total of 11 patients quit the program because of emerging disease [cardiovascular (n=6), pulmonary (n=1), orthopedic (n=2), or renal insufficiency (n=1)], or death (n=1, ruptured abdominal aortic aneurysm).

Data for the remaining 56 patients were used to analyze the change in walking distance over the 6-month study period. The baseline characteristics are shown in Table 1 and no statistical difference compared to the withdrawals was found in characteristics, with exception of the presence of hypercholesterolemia (p=0.02) and a prior neurovascular event (p=0.02). Of the 56 patients, two (3.6%) had severe chronic heart failure. Based on this cardiac co-morbidity, both patients were referred for supervised exercise

therapy to the department of physiotherapy and rehabilitation in our hospital instead of to a community-based physiotherapist.

Walking distances

At baseline, the mean ICD was 395 m (range: 55–1600 m) with a mean ACD of 563 m (range: 60–1700 m). After 3 months of supervised exercise therapy, these values improved to a mean ICD of 840 m (range: 180–2260 m) and a mean ACD of 1154 m (range: 290–3740 m). The means for both distances further increased after 6 months, with a mean ICD of 1005 m (range: 210–3810 m) and a mean ACD of 1312 m (range: 270–3980 m).

Translating these results to percentage increases, ICD increased 187% and ACD increased 142% after 3 months. After 6 months, ICD had increased 240% from the initial reading, and ACD 191% (Table 2).

Community-based versus clinic-based supervised exercise therapy

There are earlier studies reporting ACD results after supervised exercise therapy compared to non-supervised exercise therapy in patients with intermittent claudication^{4,6-8,14-16}; however, in these studies, supervised exercise therapy was provided in a clinic-based setting and sample sizes were small (range: 8–28 subjects). To compare these results with those of our community-based supervised exercise therapy study, we summarized the reported ACD or absolute claudication time (ACT) of the clinic-based supervised exercise therapy groups for each follow-up time point. For each trial, the percentage increase in ACD or ACT was calculated as shown in Table 3. After 3 months of clinic-based supervised exercise therapy, increases between 35.3% and 137.0% were found, with a mean increase of 76%. After 6 months, an increase of 90% occurred (range: 42%–159%).

Discussion

Supervised exercise therapy provided in a patient's home neighborhood in a so-called community-based physiotherapeutic setting resulted in a highly statistically significant improvement in ACD after 3 and 6 months. These results support the results of the earlier mentioned Cochrane review comparing supervised exercise therapy with non-supervised exercise therapy, showing clinical relevant differences in improvement of ACD after supervised exercise therapy.⁵ Although a comparison of our favorable results with historical studies should be regarded with caution because of the variability in the prescribed exercise regimens and treadmill walking tests used, supervised exercise therapy in a community-based setting seems to be at least as efficacious as the programs provided in a clinical setting.^{4,6-8,14-17}

A difference between the clinic-based supervised exercise therapy studies and our cohort may result from the fact that our patients received supervised exercise therapy during the entire 6 months, whereas the exercise period in three out of seven of the earlier studies lasted only 3 months.

Because we studied consecutive patients who were routinely referred to this new community-based supervised exercise program, we were able to document carefully the reasons for program discontinuation, as can also be done in routine clinical practice. In our case, 37 patients (39.8%) who were referred to the community-based supervised exercise therapy did not continue the program for a full, 6-month period. Approximately a quarter of these patients stopped because of intercurrent diseases, while for another quarter, supervised exercise therapy did not lead to adequate improvement and the patients had to undergo a vascular intervention. Overall, our recorded withdrawal rate seems to be comparable to those of trials studying supervised exercise therapy in a clinic-based setting, which reported drop-out rates of up to 43%.^{4,6,7}

One of the possible pitfalls of community-based supervised exercise therapy is the use of numerous physiotherapeutic practices (30) and physiotherapists (41), which results in a lower patient volume for each physiotherapist than occurs in a clinic-based setting. Consequently, this could lead to the inability to build experience. For this reason, we decided to implement a NETP and refer patients only to physiotherapists who participate in this network, instead of to any physiotherapist. Regular training sessions with all participating physiotherapists in the NETP ensures shared knowledge and experience. In addition, community-based supervised exercise therapy creates a larger capacity compared to clinic-based supervised exercise therapy, which means that a greater number of patients with intermittent claudication can be treated.

Percutaneous transluminal angioplasty (PTA) of iliac artery stenoses showed a weighted average 12-months patency rate of 78%¹⁸, whereas PTA of the femoropopliteal artery stenosis showed a weighted average primary patency rate at 12 months of 61%.¹⁸ Our results with a 60% success rate, which might even be higher when included "successful" drop-outs, this is comparable with the 12-months results of the interventional therapy of intermittent claudication.

In the Netherlands, reimbursement of supervised exercise therapy is currently not a main issue for most patients. The main difficulty of implementing supervised exercise therapy seems to be convincing physicians that supervised exercise therapy is superior to non-supervised exercise therapy; this difficulty is compounded by the fact that the Dutch guidelines for general practitioners for PAD (2003)¹⁹ and the guidelines for PAD of the Dutch Society of Surgery (2005)¹⁰ advise starting non-supervised exercise therapy instead of supervised exercise therapy. This advice probably persists because a Cochrane review, showing a significant difference in increase between supervised and non-supervised exercise therapy in favour of the supervised group, had not yet appeared when these guidelines were developed.⁵ Currently a prospective, multi-center trial (Exercise Therapy for Peripheral Arterial Disease (EXITPAD)) is being performed, studying the (cost-) effectiveness of supervised exercise therapy in a community-based setting compared to non-supervised exercise therapy.

Conclusion

Supervised exercise therapy in a community-based setting seems a promising approach to providing conservative treatment for patients with intermittent claudication.

Once the reproducibility of our results has been established in other parts of the Netherlands, for example in the ongoing EXITPAD study or by initiatives elsewhere, the possibilities for implementing community-based supervised exercise therapy must be explored.

Table 1: Demographic and clinical characteristics

	Analyzed population (n=56)	Withdrawals (n=37)	Significance
Age (y), mean (SD)	64.0 (10.4)	64.7 (10.8)	NS
Men, n (%)	35 (62.5)	25 (67.6)	NS
BMI, mean (SD)	26.3 (3.9)	26.1 (3.9)	NS
Current smokers, n (%)	24 (42.9)	11 (29.7)	NS
Ever smoked, n (%)	19 (33.9)	13 (35.1)	NS
Never smoked, n (%)	13 (23.2)	10 (27.0)	NS
Hypertension, n (%)	45 (80.4)	31 (83.8)	NS
Diabetes mellitus, n (%)	23 (41.1)	13 (35.1)	NS
Hypercholesterolemia, n (%)	49 (87.5)	26 (70.3)	P=0.021
Coronary heart disease, n (%)	16 (28.6)	9 (24.3)	NS
Stroke or TIA, n (%)	4 (7.1)	9 (24.3)	P=0.019
COPD, n (%)	9 (16.1)	4 (10.8)	NS
ABI, mean (SD)	0.73 (0.18)	0.70 (0.14)	NS

ABI: ankle brachial index; NS: not significant; BMI: body mass index; COPD: chronic obstructive pulmonary disease; SD: standard deviation; TIA: transient ischemic attack.

Table 2: Mean percentage increase in walking distances

Follow-up	ICD		ACD	
	Mean % (SD)	Range (%)	Mean % (SD)	Range (%)
1 month	80.9 (402.0) P < .0001	-53.9-579.0	73.8 (105.5) P < .0001	-32.1-515.4
3 months	187.3 (187.1) P < .0001	-25.5-772.7	142.2 (150.0) P < .0001	-24.8-728.3
6 months	240.2 (284.2) P < .0001	-39.8-1282.5	190.6 (229.5) P < .0001	-22.9-1187.6

ACD: absolute claudication distance; ICD: initial claudication distance; SD: standard deviation.

Table 3: Increase in ACD or ACT in prior studies using supervised ET in primary claudicants

Trial	Number of patients	Duration of supervised ET therapy (months)	Increase in ACD or ACT (%)	
			3 months	6 months
Cheetham ⁶	28	6	66.6	128.8
Degischer ¹²	19	3	82.4	70.4
Kakkos ⁷	8	6	—	51.7
Savage ¹⁴	11	6	59.8	42.3
Nielsen ⁸	25	3	35.3	—
Patterson ⁴	25	3	75.5	158.9
Regensteiner ¹³	10	3	137.0	—
Mean % increase overall			76.1	90.4

ACD: absolute claudication distance; ACT: absolute claudication time; ET: exercise therapy.

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10

Supervised exercise therapy for recurrent complaints of intermittent claudication after a previous successful vascular intervention: low risks and high yield

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Abstract

Introduction: The effect of exercise therapy in subjects with recurrent complaints of intermittent claudication after a previous vascular intervention is unknown. This pilot study explores the clinical benefit of supervised exercise therapy provided in a community-based setting in patients with peripheral arterial disease (PAD) with recurrent complaints of intermittent claudication after a previous successful peripheral vascular intervention.

Methods: Consecutive patients with PAD, returning to the vascular surgery outpatient clinic with recurrent complaints of intermittent claudication after a previous vascular intervention and sufficient command of the Dutch language, were eligible. Patients were included if the previous intervention was over one year ago, and the re-stenosis was $\geq 50\%$ of the lumen. Exclusion criterion was the inability to walk the baseline treadmill measurement for a minimum of 10 meters. The intervention was supervised exercise therapy in a community-based setting. A progressive treadmill test at baseline and at 1, 3, and 6 months of follow-up measured the initial claudication distance (ICD) and absolute claudication distance (ACD). Changes were calculated using the mean percentages of change.

Results: From January to December 2005, 23 consecutive patients with recurrent complaints of intermittent claudication were included. Three patients (13.0%) dropped out between one and 6 months. In 6 patients (26.1%) supervised exercise therapy was not able to relieve symptoms sufficiently, resulting in a vascular re-intervention.

The mean percentage of increase of the ICD was 316% after 3 months and 411% after 6 months of follow up. The increase in ACD at 3 and 6 months was 299% and 317%, respectively.

Conclusion: This pilot study shows that patients with a previous vascular intervention and recurrent complaints of intermittent claudication may significantly benefit from supervised exercise therapy. The walking distances showed a large significant increase over a period of 6 months.

Introduction

Lower-extremity revascularisation procedures in patients with peripheral arterial disease (PAD) are known to have an important rate of failure due to re-stenosis or re-occlusion over time.¹ Complaints of intermittent claudication may reoccur in case of patency failure. It is likely that a re-intervention is the first option of treatment, relieving the complaints by reperfusion of the extremity. However, in some patients a re-intervention is not feasible due to technical limitations or high risk of morbidity and/or mortality. To our knowledge, the effect of supervised exercise therapy for such patients with recurrent complaints of intermittent claudication is unknown.

Supervised exercise therapy implies adequate coaching to increase the maximal walking distance as well as coaching in the necessary changes in life-style, such as smoking cessation, weight control and increase in overall exercise. Providing supervised exercise therapy in a clinic-based setting appeared to give several restrictions. One of them is the limited capacity of the in-hospital department of rehabilitation and physiotherapy. Three sessions of 30 minutes weekly per patient appeared to be time consuming in an already busy department. Consequently, only a limited amount of patients could be offered clinic-based supervised exercise therapy. Furthermore, transport to and from the hospital, especially using public transportation, was costly for many patients, as well as time consuming. Especially the initial phase of two to three sessions weekly appeared to be problematic for a majority of patients. Some of them were too tired arriving at the hospital to start training at all.

Based on this experience a new community-based concept of supervised exercise therapy was developed and implemented, resulting in the so called Network for Exercise Therapy, Parkstad (NETP).² We hypothesised that the community-based concept of well distributed physiotherapeutic practices offers supervised exercise therapy closer to patients' homes and consequently lowers transport costs and time. The NETP consists of 29 physiotherapeutic practices equally dispersed over the southeastern part of Limburg, as well as the department of rehabilitation and physiotherapy in our hospital. By using 30 practices, the capacity problem was addressed as well.

This study explores the clinical benefit of supervised exercise therapy provided in the community-based NETP, in patients with PAD who returned with complaints of intermittent claudication after a previous successful peripheral vascular intervention.

Patients and methods

Study population

Patients with PAD, returning to the vascular surgery outpatient clinic with recurrent complaints of intermittent claudication after a previous vascular intervention longer than one year ago, and sufficient command of the Dutch language, were eligible. These patients were evaluated with the use of Doppler/treadmill examination, duplex examination, and/or angiography. Patients could be included if a re-stenosis of 50% or more or a re-occlusion of the previously treated vascular section was found, and when a re-intervention was not the first choice of treatment. Reasons why re-intervention was

not the first choice of treatment were minor complaints (e.g. claudication distance more than 500 meters) or when the risks of morbidity and mortality due to a re-intervention were considered to outweigh the severity of complaints. Exclusion criteria were a previous angioplasty or arterial surgery within the previous 12 months and the inability to walk the baseline treadmill measurement for a minimum of 10 meters. All patients received a platelet inhibitor and a statin following the Dutch guideline on PAD from the Dutch Association of Surgery.³ Patients were included from January to December 2005.

Measurements

At baseline, the ankle brachial index was measured at the vascular laboratory and vascular risk factors were registered by the vascular surgeon and/or the vascular nurse practitioner, e.g. smoking, diabetes, hypertension, hypercholesterolemia, previous myocardial infarction, history of angina pectoris, and a prior stroke. Smoking was recorded as current, former, and never. Diabetes was present if the serum fasting glucose level was ≥ 6.0 mmol/l and/or if glucose lowering medication was prescribed. A blood pressure of $\geq 140/90$ mmHg, and/or the use of antihypertensive medication were defined as hypertension, and hypercholesterolemia as a serum total cholesterol of ≥ 5.0 mmol/l and/or the use of cholesterol lowering medication. Furthermore, the primary performed vascular intervention, e.g. percutaneous transluminal angioplasty (PTA) or bypass, as well as the location were registered. The walking distances were measured by the training physiotherapist, using a progressive treadmill exercise test with a constant walking speed of 3.2 km/h beginning at 0% grade and increasing grade by 2% every 2 minutes. The outcomes for walking distance were the initial claudication distance (ICD), defined as the moment that the patient preferred to quit due to complaints of intermittent claudication in case no supervision was provided, and the absolute claudication distance (ACD) defined as the maximal walking distance. At baseline, 1 month, 3, and 6 months of follow-up the ICD and ACD were measured.

Exercise program

Supervised exercise therapy was administered according to the guidelines of the Royal Dutch Society for Physiotherapy.⁴ The mode of exercise was mainly treadmill walking up to maximal pain, alternated by other cardiovascular training and strength training. During the training sessions walking patterns were corrected to ameliorate the quality of walking. In general, patients received two to three supervised exercise sessions of approximately 30 minutes a week during the initial phase, followed by once every two weeks to once every month. Additionally, patients were encouraged to exercise daily by walking as much as possible to near maximal pain.

Statistical analyses

The primary outcome measurement was change in ACD, expressed as the percentage increase of walking distance compared to baseline. Secondly, the ICD was taken into account. For each patient the increase in ACD and ICD was calculated. The statistical significance of the increase of the ACD and ICD was compared using the paired Students'

T-test, whereas a p-value of 0.05 or lower was considered to be statistically significant. If a vascular re-intervention was performed during the period of supervised exercise therapy, the patient was excluded from further analyses. Statistical analyses were performed using SPSS 11.0.

Results

From January to December 2005, 23 consecutive patients with recurrent complaints of *intermittent claudication* were included. The baseline characteristics are shown in Table 1.

The mean period of time from the primary vascular intervention until recurrent complaints occurred, was 4.4 years (range: 1–17 years). Additional examination showed a re-stenosis after a PTA in the a. iliaca communis (n=3) and a. iliaca externa (n=1), a re-stenosis after PTA in the superficial femoral artery (n=6), an occlusion after PTA in the superficial femoral artery (n=4), a re-stenosis after PTA in the popliteal artery (n=1), an occlusion of the femoro-popliteal bypass (n=5), and an occlusion of the aorto-femoral bypass (n=3).

Of the analysed population, one patient did not want a re-intervention and was referred for supervised exercise therapy. Seven patients were waiting for a vascular re-intervention. However, due to the results of 6 months supervised exercise therapy no re-intervention was necessary in 4 of these 7 patients. In 15 patients, the recurrent complaints were mild to moderate, indicating that supervised exercise therapy was the first choice of treatment instead of a re-intervention.

The mean follow-up period of the supervised exercise therapy program was 23 weeks (range: 4–26 weeks). Three patients (13.0%) dropped out between one and 6 months, due to worsening of complaints, limited walking ability due to pulmonary disease, and dissatisfaction with treadmill walking. In 6 patients (26.1%) supervised exercise therapy did not relieve symptoms sufficiently. These were referred for a re-intervention. The remaining 14 patients (60.9%) considered their improvement in walking distance satisfactory. In none of these patients a re-intervention occurred.

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Walking distances

At baseline, patients were able to walk an average ICD of 202 meters (range: 40–800 meters), with a mean ACD of 298 meters (range: 40–1000). After one month of supervised exercise therapy walking distances increased to a mean ICD of 355 meters (range: 100–1030) and a mean ACD of 483 meters (range: 100–1150). This improvement continued, resulting in a mean ICD of 490 meters (range: 120–1600) and a ACD of 711 meters (range: 162–2000) after 3 months and a mean ICD of 669 meters (range: 70–1600) with a mean ACD of 852 meters (range: 70–1800) after 6 months of supervised exercise therapy.

Patients increased their ICD with 120.5% and the ACD increased with 92% after one month of therapy. After 3 months of supervised exercise therapy the mean percentages

of increase of the ICD and ACD were 316% and 299% and 411% and 317% after 6 months, respectively.

Discussion

Our observations suggest that supervised exercise therapy provided in a community-based setting has potentially important clinical benefit for patients with recurrent complaints of intermittent claudication after a previous successful vascular intervention. Overall, in more than 60% of the patients, supervised exercise therapy was sufficiently in relieving complaints and no re-intervention was needed. This also occurred in four out of seven patients (57%) in whom a re-intervention was actually planned, but eventually unnecessary after successful exercise therapy.

At the time the primary interventions were performed in the analysed patients, there were no facilities for a supervised exercise therapy program at our site. The only non-invasive treatment option for intermittent claudication was non-supervised exercise therapy, which is usually unsuccessful in almost half of the patients.⁵ Hence, it is uncertain whether in the presence of supervised exercise therapy, the primary intervention would have been performed at all.

The alterations that occur during exercise therapy presumably stimulate an adaptive response that eventually reduces symptoms of intermittent claudication.⁶ Several plausible mechanisms are suggested for such clinical benefits. A first suggested mechanism is the formation of collateral vessels and an increased blood flow. However, the evidence for exercise-induced increases in collateral blood flow in patients with intermittent claudication is limited and inconsistent.⁶ Besides, the correlation with walking ability is typically absent⁷ or only moderate.⁸ Although it has been shown that exercise therapy increases both nitric oxide activity and muscle-capillary density⁹, studies of exercise training and endothelial vasodilator function in patients with claudication are limited. However, changes in microcirculation and endothelial function seemed to play a role.^{9,10} The haemorrheologic hypothesis describes the theory that exercise training may improve abnormal haemorrheology in patients with intermittent claudication, thereby facilitating oxygen delivery.^{7,12} However, the extent to which this mechanism contributes to the clinical improvements seen after exercise training remains unclear. Chronic ischemia leads to an accumulation of lactate and intermediates of oxidative metabolism in muscles. Changes in muscle metabolism and oxygen extraction due to exercise training has been a consistent finding^{13,14} and appear to be an important component of the training response. Muscle ischemia due to exercise to the point of calf pain, like in this study provided supervised exercise program, induces a local inflammatory and oxidant stress response, and muscle injury.^{15,16} The effect of exercise training is a lessened ischemia at any achieved workload with evidence of decreased markers of systemic inflammation.¹⁷ Hence, the small risk of muscle fibre damage is outweighed by the improvement in walking.⁶

Although all these mechanism are potential, it is unknown what the real pathophysiological mechanism is that ultimately reduces claudication symptoms.

Due to adopting a walking pattern that favours greater gait stability, the oxygen cost of walking increases over time in patients with intermittent claudication.^{18,19} It has been shown that after four months of exercise training, patients with claudication used less oxygen at a given workload²⁰, probably resulted from a reduction in claudication pain, leading to improved biomechanical efficiency. Due to the supervision of the physiotherapist as in this pilot study, it is likely that there is a higher attention for the walking pattern compared to a non-supervised program.

It is suggested that exercise training has an independent beneficial effect on atherosclerotic risk factors. Exercise training has shown to decrease triglyceride levels and increase high-density lipoprotein cholesterol levels²¹, reduce blood pressure²²⁻²⁵, maintain glycemic control in patients with type 2 diabetes^{26,27}, and reduce central adiposity²⁸⁻³⁰. Regular physical activity has the potential to improve insulin sensitivity, and to reduce the propensity to store fat in visceral depots.²¹ A small non-randomised control study with patients with intermittent claudication showed a reduction in systolic blood pressure by 6% and a lowering in total cholesterol by 5%³¹, which are the most prevalent cardiovascular risk factors in our cohort.

It could be questioned whether an increase of 316% in maximal walking distance after 6 months of exercise therapy is of clinical relevance. Conceivably, the mostly elderly patients become more independent. Since this study was not randomised, no definite conclusion can be drawn. However, the benefits of supervised exercise therapy after an initial intervention are similar in randomised clinical trials in primary claudicants without a previous intervention using a supervised exercise therapy program.³²⁻³⁸ Importantly in these primary claudicants a supervised rehabilitation program has a greater efficacy compared to non-supervised exercise therapy.³⁹ In addition, there is virtually no morbidity and mortality from exercise rehabilitation, while they occur frequently performing a vascular intervention.⁶ Reported complications after endovascular procedures or angioplasty are 3% for iliac PTA and 3% for femoropopliteal PTA,⁷ with a 30-day mortality rate of 0.5% in patients with intermittent claudication.⁴⁰ This might seem low, however is still substantially compared to exercise therapy. The mortality risk of a surgical vascular intervention, like a bypass operation, even increases up to 2 to 3%, with a risk of morbidity of 5 to 10%.⁴¹

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Conclusion

This pilot study shows that patients with a previous vascular intervention and recurrent complaints of intermittent claudication may significantly benefit from supervised exercise therapy provided in a community-based setting. The ACD showed a significant increase over a period of 6 months. A re-intervention could possibly be delayed or postponed in more than half of the patients. We are conducting further research for the long-term results of supervised exercise therapy in the population with a previous vascular intervention and to compare a re-intervention with a supervised exercise therapy program.

Table 1: Demographic and clinical characteristics of the study population

	Analysed population n=23
Age (years) – mean (SD)	65.7 (9.8)
Men – n (%)	16 (69.6)
BMI – mean (SD)	25.1 (8.2)
Current smokers – n (%)	12 (52.2)
Ever smoked – n (%)	9 (39.1)
Never smoked – n (%)	2 (8.7)
Hypertension – n (%)	19 (82.6)
Diabetes mellitus – n (%)	8 (34.8)
Hypercholesterolemia – n (%)	15 (65.2)
Coronary heart disease – n (%)	6 (26.1)
Stroke or TIA – n (%)	0 (0)
COPD – n (%)	5 (21.7)
ABI – mean (SD)	0.63 (0.22)
pta a. iliaca	4 (17.4)
pta a. femoralis	10 (43.5)
pta a. poplitea	1 (4.3)
Bypass femoro-popliteal	5 (21.7)
Bypass aorto-femoral	3 (13.0)

SD: standard deviation; BMI: body mass index; TIA: transient ischemic attack; COPD: chronic obstructive pulmonary disease

Table 2: Mean percentage of increase in walking distances

Follow-up	ICD			ACD		
	Mean meter (SD)	Mean % (SD)	Range (%)	Mean meters (SD)	Mean % (SD)	Range (%)
1 month (n=23)	355.2 (240.4)	120.5 (148.2) p=0.0004	-6.45 – 543.8	483.5 (311.8)	91.9 (106.6) p<0.0001	-8.8 – 515.4
3 months (n=17)	490.4 (403.2)	315.7 (308.4) p=0.002	6.25 – 900.0	711.1 (545.2)	299.1 (406.8) p=0.002	22.9 – 1566.7
6 months (n=14)	669.0 (468.2)	411.2 (528.6) p=0.002	0 – 900.0	851.9 (462.4)	316.7 (270.6) p=0.002	0 – 900.0

ICD: initial claudication distance; ACD: absolute claudication distance; SD: standard deviation

Figure 1: Schedule of analysed population

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General discussion

Discussion

The data presented in this thesis outlines the use of the ABI in general practice as screening measurement for the early detection of asymptomatic peripheral arterial disease (PAD) and for confirmation of the diagnosis in patients with symptoms of intermittent claudication. Furthermore, this thesis underlines the important role of conservative treatment options in patients with intermittent claudication, especially supervised exercise therapy.

Part one

The PREVALENT study: feasibility of the ankle brachial index

In subjects with symptoms suggestive of intermittent claudication, the use of a diagnostic questionnaire, that has been used in epidemiological studies, was shown to be inadequate for use in daily practice to discriminate between those with and without PAD. Although a clinical risk model was developed to easily assess the likelihood of PAD, in the lower risk group there was still a substantial part with PAD according to the ABI measurement. To leave out the ABI measurement in this lower risk population would lead to inadequate prevention of cardiovascular events. One of the implications for future clinical practice is that in all patients with symptoms suggestive of intermittent claudication, the ABI should be performed in order to diagnose PAD, despite the fact that an ABI measurement is more time-consuming than the use of a questionnaire. Although a differentiation can be made between symptomatic groups with extremely high and lower prevalences of PAD, due to the in this thesis developed clinical risk model for prediction of the diagnosis of PAD, this model will have no additional value in daily practice.

Using the ABI as a screening measurement rises a lot of practical questions to general practitioners. Although the ABI measurement was earlier reported as feasible and efficient screening measure, also in a community population¹⁻³, it will substantially increase the workload of general practitioners. In this thesis it is explored that an ABI measurement in the overall population of 50 years and older, as recommended by several current guidelines, carries the burden of a week full time work every year for a general practitioner. Although in the Netherlands every ABI measurement is reimbursed by healthcare payers, it is doubtful that the recommendations of guidelines regarding the advice to perform a risk assessment for cardiovascular morbidity and mortality are feasible and followed in general practice. However, a frequently asked question of general practitioners was an instruction, guiding them in which specific populations an ABI measurement is useful. In this thesis, a clinical prediction model has been developed, based on statistically significant vascular risk factors (e.g. age, smoking, and hypertension). This clinical prediction model can be used as a guidance tool to effectively screen a selected high risk population in daily practice for the presence of PAD, and consequently generalised atherosclerosis. For example, current smoking as a single risk factor satisfies a score of seven, independent of age, while former smokers

will only obtain this level when 65 or older, and with the presence of non-adequately treated hypertension.

Identification of asymptomatic PAD may identify those subjects who are at risk to develop vascular complications and who would otherwise not receive adequate risk factor management therapies. However, the real value of screening asymptomatic subjects for PAD in terms of risk reduction is currently not known. A documented confirmation of the presence of PAD may assist the initiation of changes of life style of patients including cessation of smoking, weight reduction, and an increase in physical exercise. On the contrary, an early diagnosis of PAD might lead to a substantial increase in medication usage with a currently unknown effect on the quality of life. Further research about the real value of screening for PAD in view of risk reduction and cost-effectiveness should be performed.

However, the advice to perform a risk assessment whether to initiate a primary prevention strategy in all asymptomatic subjects is consistent with current international clinical practice guidelines including ATP-III⁴, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC)-VII⁵, the European Guideline⁶, the American Heart Association (AHA) and American College of Cardiology (ACC) recommendations⁷, and the Dutch CBO multidisciplinary guideline of cardiovascular risk factor management.⁸ Although the ABI measurement is not included in this initial assessment, it is recommended as additional measurement in selected populations, especially in people aged 50 years and older or those who appear to be at risk, since an abnormal ABI provides incremental prognostic information. In this thesis it is calculated that a single screening of the ABI in the overall population of 50 years and older would take an investment of approximately 5 weeks of full time work. Using the earlier mentioned clinical prediction model, however, screening of the population at risk according to this model, would take approximately one-and-a-half week of full time work for an initial screening measurement by ABI. Our calculations suggest that using the clinical risk score, the work load of screening can be reduced by 60% while the majority of asymptomatic patients with PAD (63%) will be detected.

It is generally believed that a high ABI (>1.4) is related to diabetes mellitus, since generalized stiffening of blood vessels⁹, as well as medial arterial calcification¹⁰ are common in diabetic patients. Due to these mechanisms, underlying arteries become incompressible. However, this thesis showed no direct relation between the presence of diabetes and a high ABI, despite a substantial number of patients with an ABI above 1.4. Moreover, in subpopulations, none of the first-order interaction effects between diabetes and another vascular risk factor showed a statistically significant effect on the presence of a high ABI. Based on the absence of an important direct association between the presence of diabetes mellitus and a high ABI, the concept that a high ABI is often caused by diabetes mellitus should be refuted.

Part two

Conservative treatment of PAD

Although recent guidelines about the management of patients with PAD recommend exercise therapy as treatment for patients with intermittent claudication, they are not unequivocal regarding the use of supervised programs. The ACC/AHA practice guideline for the management of patients with PAD recommends a supervised exercise therapy with a level A of evidence.¹² However, the Dutch guideline of the Society of Surgery and Radiology for diagnosis and management of PAD reports that currently there is not enough evidence for the benefits of a structured supervised exercise program for patients with intermittent claudication¹³. The most frequent prescription of exercise therapy world wide is a single "go home and walk" advice. In the meta-analyses performed in this thesis, supervised exercise therapy showed to be superior compared to a non-supervised exercise therapy program.

In those circumstances that a supervised program was available, these programs were provided in a clinical-based setting, with a major restriction of a limited capacity of the in-hospital department of rehabilitation and physiotherapy. Three sessions of half an hour weekly per patient appeared time consuming in an already busy department. Furthermore, transport to and from the hospital, especially using public transportation was costly for many patients, as well as time consuming.

To improve the care for patients with intermittent claudication, a new community-based concept of supervised exercise therapy in a physiotherapeutic setting was developed and implemented.¹³ The six-months follow-up results of this community-based network of supervised exercise therapy showed a statistically significant improvement in walking distances for patients with intermittent claudication without a previous vascular intervention. One-year results will have to be waited for to show whether walking distances will increase even more or that a steady state will be reached between 6 and 12 months of supervised exercise therapy. Ideally, the effects of a supervised exercise therapy program in a physiotherapeutic setting on the long term should be translated into effects on long term morbidity and mortality. Research to determine the cost-effectiveness of supervised exercise therapy, and the effect on cardiovascular risk factors is currently undertaken by our research group, performing the national, multicentre EXITPAD study. During the initial phase of this multicentre study, we experienced that implementing new community-based networks of physiotherapists is feasible. For interested centres, a blue print of the implementation script is available at the research group.

Continuing training sessions in a home-based setting during life time, possibly in group sessions, achieved results by a supervised program could be maintained or even improved over years, stimulating the changes in life style to be durable. Furthermore, in the future should supervised exercise therapy be compared with other interventions, such as angioplasty, surgery, with or without the combination of exercise therapy, for both walking and quality of life improvement.

That exercise therapy is the first treatment of choice in primary claudicants is well known. In patients with a previous peripheral vascular intervention being referred with recurrent complaints of intermittent claudication after more than one year after the intervention, nothing was known about the value of exercise therapy as treatment option. A patient cohort with recurrent complaints of intermittent claudication presented in this thesis suggest that exercise therapy provided in a community-based supervised physiotherapeutic setting, has potentially important clinical benefit. Further research using randomised studies for the long-term results of supervised exercise therapy in the population with a previous vascular intervention should be performed, as well as comparing a re-intervention with a supervised exercise therapy program.

Conclusion

In conclusion, it can be said that the ABI measurement is used in symptomatic patients for about 40 years from now. In spite of this, it is still not known whether screening asymptomatic subjects can prevent future cardiovascular events.

Analogous to this, the benefits of exercise therapy for the treatment of intermittent claudication is known for over a century, while the exact explanation of working mechanism of exercise therapy is still unsolved. Besides, no clear prescription about the content of exercise therapy can currently be given.

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Summary

Atherosclerosis, a process of thickening and hardening of the arteries and loss of blood vessel elasticity, is a systemic disease that is most frequently associated with fatal and non-fatal myocardial infarction, stroke, and disease of the aorta and lower extremities. Peripheral arterial disease (PAD) is atherosclerosis of the lower extremities, and is an important marker for generalised atherosclerosis since it is closely associated with cardio- and cerebrovascular disease. Assessment of the ankle brachial index (ABI) is an effective diagnostic tool for PAD and is able to provide important information about subclinical atherosclerosis. The superior role of supervised exercise therapy compared to non-supervised exercise therapy is more and more recognised as valuable option in the conservative treatment of PAD. This thesis is centred on the use of the ABI in general practice, both as diagnostic measurement as well as screening measurement to detect PAD, and on the conservative treatment of PAD. The first part of the thesis outlines the PREVALENT study, showing the results of the feasibility of the ABI in general practice. In the second part discusses the possibilities of conservative treatment for PAD, especially different forms of exercise therapy.

Part one

The PREVALENT study: feasibility of the ankle brachial index

The PREVALENT study is a large observational study, conducted from October 2002 to February 2005 among 955 Dutch general practitioners. Overall, 13,038 subjects of 55 years and older with symptoms of intermittent claudication according to the general practitioner (without confirmation by ABI) and/or presenting with at least one vascular risk factor (smoking, hypertension, diabetes, and hypercholesterolemia), were included in this study. Patients were selected by the general practitioner during visiting hours and from medical records.

Chapter two describes the first part of the PREVALENT study. The aim of this part was to investigate the Edinburgh Claudication Questionnaire (ECQ) in general practice and to develop a clinical decision rule based on risk factors to be able to easily assess the likelihood of PAD in this setting. This part of the study included patients of ≥ 55 years visiting the general practitioner for symptoms suggestive of intermittent claudication or with one or more risk factor(s). The prevalence of PAD, defined as ABI < 0.9 , was related to risk factors using logistic regression analyses on which a clinical decision rule was developed and related to the presence of PAD. Of the 4,790 included patients visiting the general practitioner with symptoms suggestive of intermittent claudication, 4,527 were eligible for analyses. The prevalence of PAD in this group was 48.3%. The sensitivity of the ECQ was only 56.2%. The prevalence of PAD in the developed clinical decision rule that included age, male sex, smoking, hypertension,

hypercholesterolemia, and a positive ECQ, increased from 14% in the lowest to 76% in the highest category.

This study indicates that the ECQ alone has an inadequate diagnostic value in detecting patients with PAD. In patients with complaints suggestive of intermittent claudication the ABI should be performed to diagnose PAD, although our clinical decision rule could help to differentiate between extremely high and lower prevalences of PAD.

Chapter three presents a simple prediction rule that could be of much use to estimate the risk of an abnormal ABI. This part of the PREVALENT study included 7,454 patients of 55 years and older presenting with at least one vascular risk factor and no complaints of intermittent claudication. The prevalence of PAD, defined as an ABI below 0.9, was related to vascular risk factors using regression analyses on which the clinical prediction model was developed. The overall prevalence of PAD was 18.4%. Since the treatment of subjects with a history of coronary heart disease and cerebrovascular disease will not be influenced by the finding of asymptomatic PAD, these subjects were not taken into account for the development of the clinical prediction model. Analyses showed a significantly increased risk for PAD with increasing age, smoking, and hypertension. The clinical prediction model, giving risk factor points per factor (age: 1 point per 5 years starting at 55 years, ever smoked: 2 points, currently smoking: 7 points, and hypertension: 3 points), showed a proportional increase of the PAD prevalence with each increasing risk profile (range: 7.0%–40.6%). Based on this clinical prediction model, the general practitioner is able to identify a high risk population in which measurement of an ABI is useful.

In **Chapter four** the impact of guidelines regarding the use of ABI as a screening tool, the corresponding number needed to screen, including the required time investment, and the feasibility of ABI performance, was assessed. Data of the overall PREVALENT study were used. Guidelines were systematically searched for indications that ABI measurement should be performed. To assess the number needed to screen, a composition of the general population was made, and the time needed to perform the ABI was assessed. The number needed to screen was translated to the setting of a single general practice. Guidelines recommend the ABI as an additional measurement in selected populations (e.g. persons of 50 years and older, or those who appear to be at risk of cardiovascular disease). Approximately 10% of subjects above 55 years are without any vascular risk factor. The mean time necessary for ABI measurement was 17 minutes. Screening of the overall population of 50 years and older results in approximately 731 subjects per general practice who should be screened, resulting in a time-requirement of approximately 5 weeks of full time work. Using an existing clinical prediction model, 213 patients per general practice should be screened for PAD by ABI

measurement, corresponding to approximately 60 working hours for an initial screening measurement.

Screening the entire population of 50 years and older, as advised in clinical guidelines, will in our opinion not be feasible in general practice. A more rationale and efficient approach might be screening of subsets of the population of 55 years and older based on a clinical prediction model.

Chapter five shows the prevalence of a high ABI in relation to risk factors for atherosclerosis in a community dwelling population. Data of the overall PREVALENT study were used. The prevalence of a high ABI, defined as above 1.4, was related to vascular risk factors, using logistic regression analyses. Of the 13,038 patients included, 12,886 were eligible for analyses. The prevalence of an ABI above 1.4 was 5.2%. Although the presence of diabetes when treated inadequately was significantly related to a high ABI (Odds Ratio (OR)=1.28) using univariate analysis, this was lost using multivariate analyses ($p=0.865$). Whereas first-order interaction effects showed no effect on a high ABI, three second-order interactions showed significant effects of the presence of diabetes on a high ABI in the subgroups: elderly women and middle-aged men, men with a high diastolic blood pressure, and men with a history of cerebrovascular disease. Effects of diabetes on the measurement of a high ABI appeared to be present only in subgroups. Since no direct relation between diabetes and a high ABI was observed, the assumption that a high ABI is often caused by diabetes alone is not supported.

Part two

Conservative treatment of PAD

A state of the art review was performed in **Chapter six** to discuss the available medical therapies for PAD, including risk factor modification and antiplatelet therapies, as well as strategies for symptomatic relief in both patients with intermittent claudication and patients with critical limb ischemia. In general, risk factor modification and antiplatelet therapy is essential in all patients with PAD to prevent systemic atherosclerotic complications. Furthermore, for symptomatic relief exercise therapy is the main intervention while pharmacological treatment should be only complementary in patients with intermittent claudication. In patients with critical limb ischemia, when revascularization therapy is not possible, an attempt should be made to avoid amputation with conservative treatment using analgesics, vasodilators and/or anticoagulants. In case of an acute onset of critical limb ischemia, thrombolysis is indicated.

Chapter seven presents a meta-analysis to evaluate the effects of supervised versus non-supervised exercise therapy on the maximal walking time or distance for people with intermittent claudication. Randomized and controlled clinical trials comparing supervised exercise programs with non-supervised exercise programs for people with intermittent claudication were included for analyses. For all continuous outcomes we extracted the number of participants, the mean differences, and the standard deviation. If data were available, the standardized mean difference was calculated using a fixed-effect model. Twenty-seven trials were identified, of which 19 had to be excluded because the control group received no exercise therapy at all. The remaining eight trials involved a total of 319 male and female participants with intermittent claudication. The follow up ranged from 12 weeks to 12 months. In general, the supervised exercise regimens consisted of three exercise sessions per week. All trials used a treadmill walking test as one of the outcome measures. The overall quality of the included trials was good, though the trials were all small with respect to the number of participants, ranging from 20 to 59. Supervised exercise therapy showed statistically significant and clinically relevant differences in improvement of maximal treadmill walking distance compared with non-supervised exercise therapy regimens, with an overall effect size of 0.58 (95% confidence interval 0.31 to 0.85) at three months. This translates to a difference of approximately 150 meters increase in walking distance in favor of the supervised group. Supervised exercise therapy is suggested to have clinically relevant benefits compared with non-supervised regimens, which is the main prescribed exercise therapy for people with intermittent claudication. However, the clinical relevance has not been demonstrated definitely and will require additional studies with a focus on the improvements in quality of life.

In **Chapter eight** several possibilities in providing exercise therapy are evaluated and compared. First, as shown earlier, supervised exercise therapy programs have significant benefits compared with non-supervised programs. Supervised programs as described in literature so far were provided in a clinic-based setting. Compared to clinic-based programs community-based supervised exercise therapy has both economic and logistic advantages, due to differences in capacity, transport costs, and time consume. Based on this knowledge, a new community-based concept of supervised exercise therapy was developed and implemented: the so called Network of Exercise Therapy, Parkstad. Community-based supervised exercise therapy programs seems to be as effective as supervised exercise therapy provided in a clinic-based setting and is a promising approach to providing conservative treatment for patients with intermittent claudication. Supervised exercise therapy in a community-based setting should ideally be the initial standard of care for patients with intermittent claudication, however, a study of the cost-effectiveness should be awaited.

Chapter nine was to determine the effect of supervised exercise therapy provided in a community-based setting on walking distances. This cohort study included all consecutive patients presenting at the vascular outpatient clinic with intermittent claudication, diagnosed by a resting ABI below 0.9, who had no previous peripheral vascular intervention for PAD, no major amputation, and sufficient command of the Dutch language. The exclusion criterion was the inability to walk the baseline treadmill test for a minimum of 10 meters. A progressive treadmill test at baseline and at 1, 3, and 6 months of follow-up measured initial claudication distance and absolute claudication distance. Changes were calculated using the mean percentages of change. From January through October 2005, 93 consecutive claudicants were eligible. Overall, 37 patients discontinued the supervised exercise therapy program. Eleven of these patients stopped because of intercurrent diseases, while for 10 supervised exercise therapy did not lead to adequate improvement and underwent a vascular intervention. Three patients quit the program stating that they were satisfied with the regained walking distance and did not require further supervised exercise therapy. Ten patients were not motivated sufficiently to continue the program, and in three patients, a lack of adequate insurance coverage was the reason for dropping out. Data for 56 patients were used, showing a mean percentage increase in initial claudication distance of 187% and 240% after 3 and 6 months, respectively. Mean percentage of the absolute claudication distance increased 142% and 191% after 3 and 6 months, respectively. Supervised exercise therapy in a community-based setting is a promising approach to providing conservative treatment for patients with intermittent claudication.

In **chapter ten** the clinical benefit of supervised exercise therapy provided in a community-based setting in patients with PAD with recurrent complaints of intermittent claudication after a previous successful peripheral vascular intervention was explored. Consecutive patients with PAD, returning to the vascular surgery outpatient clinic with recurrent complaints of intermittent claudication after a previous vascular intervention and sufficient command of the Dutch language, were eligible. Patients were included if the previous intervention was over one year ago, and the re-stenosis was $\geq 50\%$ of the lumen. Exclusion criterion was the inability to walk the baseline measurement for a minimum of 10 meters. A progressive treadmill test at baseline and at 1, 3, and 6 months of follow-up measured the initial claudication distance and absolute claudication distance. Changes were calculated using the mean percentages of change. From January to December 2005, 23 consecutive patients with recurrent complaints of intermittent claudication were included. Three patients (13.0%) dropped out between one and 6 months. In 6 patients (26.1%) supervised exercise therapy was not able to relief symptoms sufficiently, resulting in a vascular re-intervention. The mean percentage of increase of the initial claudication distance

was 316% after 3 months and 411% after 6 months of follow up. The increase in absolute claudication distance at 3 and 6 months was 299% and 317%, respectively. This pilot study shows that patients with a previous vascular intervention and recurrent complaints of intermittent claudication may significantly benefit from supervised exercise therapy. The walking distances showed a large significant increase over a period of 6 months.

PAD often remains unrecognized because most physicians and patients are unaware of the potential presence, as well as the dangers of this disease. Patients with PAD, regardless of symptoms status, should achieve a risk reduction aimed at specific treatment targets comparable to individuals with established coronary artery disease. Our developed PREVALENT clinical prediction model offers general practitioners an effective tool to effectively screen the population at risk. As main conservative treatment, exercise therapy should worldwide be available in a supervised, community-based setting for all patients with symptomatic PAD. With this, interventions with a higher morbidity and mortality chance can be prevented.

Samenvatting

Atherosclerose is een gegeneraliseerde aandoening van verdikking en verharding van de arteriën met een afname van de elasticiteit. Het is met name geassocieerd met myocard- en cerebraal infarct, aandoeningen van de aorta en onderste extremiteiten. Perifeer arterieel vaatlijden (PAV) is een vorm van atherosclerose in de onderste extremiteiten en is, gezien de nauwe associatie met cardio- en neurovasculaire aandoeningen, een belangrijke marker voor gegeneraliseerd atherosclerose. Bepaling van de enkel-arm-index (EAI) is een effectief diagnostisch instrument om PAV vast te stellen en geeft daarmee belangrijke informatie over subklinische vormen van atherosclerose. De belangrijke rol van gesuperviseerde looptherapie wordt meer en meer erkend als waardevolle therapieoptie bij de conservatieve behandeling van PAV.

Dit proefschrift concentreert zich op het gebruik van de EAI in de huisartsenpraktijk, zowel als diagnostisch meetinstrument als in de vorm van screening om PAV vast te stellen. Daarnaast wordt de conservatieve behandeling van PAV uitgebreid belicht. Het eerste deel van het proefschrift beschrijft de resultaten van de PREVALENT waarin onder andere de resultaten van de uitvoerbaarheid van de EAI in de algemene huisartspraktijk wordt getoond. In het tweede deel wordt de conservatieve behandeling van PAV besproken en dan met name de verschillende vormen van looptherapie.

Deel 1

De PREVALENT studie: uitvoerbaarheid van de enkel-arm-index

De PREVALENT studie is een grote observationele studie, uitgevoerd van oktober 2002 tot en met februari 2005 onder 955 Nederlandse huisartsen. In totaal werden in deze studie 13.038 mensen geïnccludeerd van 55 jaar of ouder met symptomen van claudicatio intermittens volgens de huisarts (zonder bevestiging van de EAI) en/of met minstens een vasculaire risicofactor (roken, hypertensie, diabetes en hypercholesterolemie). De deelnemers werden geselecteerd door de huisarts tijdens het spreekuur en vanuit de medische status.

Hoofdstuk twee beschrijft het eerste deel van de PREVALENT studie. Het doel van dit deel was enerzijds om de Edinburgh Claudicatio Vragenlijst in de huisartsenpraktijk te onderzoeken en anderzijds om een klinisch beslissingsmodel te ontwikkelen, gebaseerd op risicofactoren, om zo eenvoudig de waarschijnlijkheid van PAV te kunnen bepalen. Voor dit deel van de studie werden patiënten geïnccludeerd van 55 jaar of ouder die de huisarts bezochten met symptomen die suggestief zijn voor claudicatio intermittens of met een of meer risicofactoren. De prevalentie van PAV, gedefinieerd als een $EAI < 0,9$, werd gerelateerd aan risicofactoren door middel van logistische regressie analyses. Op basis van deze analyses werd een klinisch beslissingsmodel ontwikkeld welke werd gerelateerd aan de aanwezigheid van PAV. Van de 4.790 geïnccludeerde patiënten die de huisarts bezochten met symptomen suggestief voor claudicatio intermittens, waren uiteindelijk 4.527 geschikt voor de analyses. De prevalentie van PAV in deze groep was 48,3%. De sensitiviteit van de Edinburgh Claudicatio Vragenlijst was slechts 56,2%.

Het klinische beslissingsmodel werd samengesteld uit de significante risicofactoren leeftijd, mannelijk geslacht, roken, hypertensie, hypercholesterolemie en een positieve Edinburgh Claudicatio Vragenlijst. De prevalentie van PAV in dit model nam toe van 14% in de laagste tot 76% in de hoogste risicocategorie. Deze studie indiceert dat de Edinburgh Claudicatio Vragenlijst alleen een inadequate diagnostische waarde heeft voor het bepalen van patiënten met PAV. Bij patiënten met symptomen suggestief voor claudicatio intermittens zou altijd de EAI gemeten moeten worden om de diagnose PAV vast te kunnen stellen. Het klinische beslissingsmodel kan echter dienen ter differentiatie tussen extreem hoge en extreem lage prevalenties van PAV.

Hoofdstuk drie toont een eenvoudig te gebruiken voorspellend model welke nuttig zou kunnen zijn voor het bepalen van het risico op een afwijkende EAI. Voor dit deel van de PREVALENT studie werden 7.454 patiënten geïnccludeerd van 55 jaar of ouder met minimaal een vasculaire risicofactor en zonder klachten van claudicatio intermittens. De prevalentie van PAV, gedefinieerd als een EAI lager dan 0,9, werd gerelateerd aan vasculaire risicofactoren door middel regressie analyses op basis waarvan een klinisch voorspellend model werd ontwikkeld. De totale prevalentie van PAV was 18,4%. Aangezien de behandeling van patiënten met een voorgeschiedenis van een cardiovasculaire dan wel neurovasculaire aandoening niet beïnvloed zal worden door het diagnosticeren van asymptomatisch PAV, werden deze patiënten buiten ogenschouw gelaten bij het ontwikkelen van het klinisch voorspellende model. Analyses toonden een significante stijging van het risico voor PAV bij een toename van de leeftijd, roken en hypertensie. In het klinisch voorspellende model worden risicofactor punten gegeven per factor (leeftijd: 1 punt per 5 jaren beginnend bij 55 jaar, ooit gerookt: 2 punten, huidige rokers: 7 punten, hypertensie: 3 punten). Dit model toont een proportionele stijging van de PAV prevalentie bij elke toegenomen risicoprofiel (range: 7,0%–40,6%). Gebaseerd op dit klinisch voorspellende model is de huisarts in staat om op eenvoudige wijze een hoog risico populatie te identificeren bij wie het meten van de EAI nuttig is om vroegtijdige atherosclerose te ondervangen.

In **hoofdstuk vier** worden de volgende punten onderzocht: de invloed van richtlijnen met betrekking tot het gebruik van de EAI als screenend instrument, corresponderende aan deze aanbevelingen het aantal te screenen mensen, inclusief de tijdsinvestering die hiermee samen gaat, en de uitvoerbaarheid van de EAI meting. Hiervoor werd de totale dataset van de PREVALENT studie gebruikt. Richtlijnen werden systematisch onderzocht op indicaties voor het meten van de EAI. Om het aantal te screenen mensen vast te kunnen stellen werd een compositie van de algemene populatie gemaakt. Daarnaast werd de tijdsinvestering welke nodig is om een EAI uit te voeren bepaald. Het aantal te screenen mensen werd vertaald naar een algemene huisartsenpraktijk. Richtlijnen bevelen de EAI aan als additionele meting in geselecteerde populaties (personen van 50 jaar of ouder of personen met een verhoogd cardiovasculair risico). Ongeveer 10% van de populatie ouder dan 55 jaar is niet bekend met een vasculaire risicofactor. De gemiddelde tijdsinvestering die nodig is om een enkele EAI te meten

bedroeg 17 minuten. Screenen van de algemene populatie van 50 jaar en ouder betekent dat circa 731 patiënten per huisartsenpraktijk gescreend zouden moeten worden, resulterend in een tijdsinvestering van circa 5 fulltime werkweken. Wanneer gebruik gemaakt wordt van een bestaand klinisch voorspellend model zouden 213 patiënten gescreend moeten worden voor PAV door middel van de EAI meting. Dit komt overeen met circa 60 werkuren voor een initiële screeningsmeting. Screenen van de totale populatie van 50 jaar of ouder, zoals aanbevolen wordt in klinische richtlijnen, is naar onze mening niet uitvoerbaar in de algemene huisartsen praktijk. Een meer rationele en efficiëntere benadering zou zijn wanneer slechts een risicovol deel van de populatie, gebaseerd op een klinisch voorspellend model, zou worden gescreend.

Hoofdstuk vijf toont de prevalentie van een hoge EAI in relatie tot risicofactoren voor atherosclerose in de algemene populatie. De totale dataset van de PREVALENT studie werd hiervoor gebruikt. De prevalentie van een hoge EAI, gedefinieerd als hoger dan 1,4, werd gerelateerd aan vasculaire risicofactoren door middel van logistische regressie analyse. Van de 13.038 geïncludeerde patiënten waren 12.886 geschikt voor verdere analyse. De prevalentie van een EAI hoger dan 1,4 was 5,2%. Ondanks de bevinding dat de aanwezigheid van diabetes, wanneer het inadequaet gereguleerd werd, significant gerelateerd was aan een hoge EAI (odds ratio (OR)=1,28) in de univariabele analyse, verdween deze significantie in de multivariabele analyse ($p=0,865$). Hoewel eerste-order interactie effecten geen significant effect op een hoge EAI aantoonden, werden een drietal significante tweede-order interacties aangetoond tussen de aanwezigheid van diabetes en een verhoogde EAI. Deze effecten werden aangetoond in de volgende subgroepen: oudere vrouwen en mannen van middelbare leeftijd, mannen met een hoge diastolische bloeddruk en mannen met een neurovasculaire aandoening in de voorgeschiedenis. Effecten van diabetes op de uitkomstmeting van een hoge EAI lijken slechts aanwezig te zijn in enkele subgroepen. Aangezien geen directe relatie tussen diabetes en een hoge EAI kon worden vastgesteld, kan de veronderstelling dat een hoge EAI vaak alleen veroorzaakt wordt door diabetes niet worden ondersteund.

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Deel twee

Conservatieve behandeling van perifeer arterieel vaatlijden

Een review over de huidige stand van zaken met betrekking tot de beschikbare medicamenteuze behandelingen voor PAV wordt beschreven in **hoofdstuk zes**. Hierin komen zowel risicofactor management en het gebruik van trombocyten aggregatie remmers, als behandelingsmogelijkheden om symptomen te verminderen voor zowel patiënten met claudicatio intermittens als voor patiënten kritieke ischemie van de benen aan bod. In het algemeen zijn risicofactor management en de behandeling met trombocyten aggregatie remmers een essentieel onderdeel van de behandeling van alle patiënten met PAV om zo systemische complicaties van atherosclerose te voorkomen. Daarnaast is looptherapie de belangrijkste interventie om de symptomen van claudicatio intermittens te verminderen, terwijl farmacologische behandelingen slechts als aanvullende therapie gebruikt zouden moeten worden. Bij patiënten met

kritieke ischemie in de benen, waarbij behandeling door middel van revascularizatie niet mogelijk is, zou gebruik gemaakt moeten worden van analgetica, vasodilatoren en/of anticoagulantia om zo een amputatie te vermijden. Thrombolyse is geïndiceerd wanneer sprake is van acute kritieke ischemie.

Hoofdstuk zeven presenteert een meta-analyse waarin de effecten van gesuperviseerde versus niet-gesuperviseerde looptherapie op de maximale loopafstand of tijd worden geëvalueerd bij patiënten met claudicatio intermittens. Gerandomiseerde en gecontroleerde klinische studies, welke gesuperviseerde looptherapie programma's vergelijken met niet-gesuperviseerde looptherapie programma's voor patiënten met claudicatio intermittens, werden geïnccludeerd voor analyse. Voor alle continue variabelen werden het aantal deelnemers, het gemiddelde verschil en de standaard deviatie geëxtraheerd. Wanneer data beschikbaar waren, werd het gestandaardiseerde gemiddelde verschil berekend door middel van een gefixeerd-effect model. Zevenentwintig studies werden geïdentificeerd, waarvan 19 geëxcludeerd moesten worden aangezien de controle groep geen looptherapie kreeg. De resterende acht studies bestond in totaal uit 319 mannelijke en vrouwelijke deelnemers met claudicatio intermittens. De follow-up varieerde van 12 weken tot 12 maanden. In het algemeen bestonden de gesuperviseerde looptherapie programma's uit drie therapiesessies per week. Alle studies maakten gebruik van een loopbandtest als een van de uitkomstmetingen. De algemene kwaliteit van de geïnccludeerde studies was goed, hoewel de studies klein waren met betrekking tot het aantal deelnemers, variërend van 20 tot 59. Gesuperviseerde looptherapie toonde statistisch significante en klinisch relevante verschillen in verbetering van maximale loopafstand vergeleken met niet-gesuperviseerde looptherapie programma's, met een totale effectgrootte van 0,58 (95% betrouwbaarheidsinterval 0,31 tot 0,85) na 3 maanden. Dit is te vertalen naar een verschil van circa 150 meter toename in loopafstand in het voordeel van de gesuperviseerde groep.

Gesuggereerd wordt dat gesuperviseerde looptherapie klinisch relevante voordelen heeft ten opzichte van niet-gesuperviseerde programma's, terwijl dit laatste de meest voorgeschreven vorm van looptherapie is voor patiënten met claudicatio intermittens. Echter, de klinische relevantie kon niet helemaal bewezen worden. Hiervoor zullen aanvullende studies nodig zijn die zich concentreren op de verbeteringen in kwaliteit van leven.

In **hoofdstuk acht** worden verschillende mogelijkheden van looptherapie besproken en vergeleken. Ten eerste, zoals eerder reeds aangetoond, hebben gesuperviseerde looptherapie programma's significante voordelen vergeleken met niet-gesuperviseerde programma's. Gesuperviseerde programma's zoals beschreven in de literatuur tot nog toe werden allen verzorgd in een klinische setting. Vanwege verschil in capaciteit, transport kosten en tijdsinvestering heeft gesuperviseerde looptherapie verzorgd in een regionale setting ten opzichte van de klinische setting zowel economische als logistieke voordelen. Op basis van deze kennis werd een nieuw regionaal gebaseerd concept

van gesuperviseerde looptherapie ontwikkeld en geïmplementeerd: het zogenaamde Netwerk LoopTherapie Parkstad (NLTP). Regionale looptherapie programma's lijken net zo effectief te zijn als gesuperviseerde looptherapie gegeven in een klinische setting en is een veelbelovende benadering voor het aanbieden van de conservatieve behandeling aan patiënten met claudicatio intermittens. Gesuperviseerde looptherapie in een regionale setting zou idealiter de initiële standaardbehandeling moeten zijn voor patiënten met claudicatio intermittens, hoewel een studie naar de kosteneffectiviteit afgewacht zou moeten worden.

In **hoofdstuk negen** worden de effecten bepaald van gesuperviseerde looptherapie gegeven in een regionale setting op de loopafstand. In deze cohort studie werden alle opeenvolgende patiënten die zich presenteerden met claudicatio intermittens op de polikliniek vaatchirurgie, gediagnosticeerd door middel van een EAI lager dan 0,9, geïnccludeerd. Exclusie criteria waren een eerdere perifere vasculaire interventie vanwege PAV, grote amputatie, onvoldoende kennis van de Nederlandse taal en het niet in staat zijn om verder dan 10 meter te lopen tijdens de eerste loopbandtest. Door middel van een progressieve loopbandtest werden aan het begin en na 1, 3 en 6 maanden follow-up zowel de initiële claudicatio afstand als de absolute claudicatio afstand gemeten. Veranderingen in loopafstand werden berekend door middel van het gemiddelde percentage verandering. Van januari tot en met oktober 2005 waren 93 opeenvolgende claudicanten geschikt voor deelname aan de studie. In totaal beëindigden 37 patiënten het gesuperviseerde looptherapie programma. Elf van deze patiënten stopten vanwege een niet-vasculaire gerelateerde additionele aandoening. Bij 10 patiënten leidde de looptherapie niet tot een adequate verbetering van de symptomen en ondergingen om deze reden een vasculaire interventie. Drie patiënten stopten omdat ze naar eigen zeggen tevreden waren met de behaalde loopafstand en geen verdere gesuperviseerde looptherapie meer nodig hadden. Tien patiënten waren onvoldoende gemotiveerd om het programma volledig te volgen en drie patiënten waren onvoldoende verzekerd waardoor ze moesten stoppen met de gesuperviseerde looptherapie.

Uiteindelijk waren data van 56 patiënten beschikbaar voor analyse, welke een gemiddelde percentage stijging van de initiële claudicatio afstand aantoonde van 187% en 240% na respectievelijk 3 en 6 maanden. Het gemiddelde percentage van de absolute claudicatio afstand steeg met 142% en 191% na respectievelijk 3 en 6 maanden. Gesuperviseerde looptherapie in een regionale setting is een veelbelovende benadering van de conservatieve behandeling van patiënten met claudicatio intermittens.

Hoofdstuk tien beschrijft het klinische voordeel van gesuperviseerde looptherapie aangeboden in een regionale setting voor patiënten met PAV met recidief klachten van claudicatio intermittens na een eerdere succesvolle perifere vasculaire interventie. Opeenvolgende patiënten met PAV die zich opnieuw meldden op de polikliniek vaatchirurgie met recidief klachten van claudicatio intermittens na een eerdere

vasculaire interventie en met voldoende kennis van de Nederlandse taal waren geschikt voor inclusie van deze studie. Patiënten werden geïnccludeerd wanneer de eerdere interventie langer dan een jaar geleden had plaats gevonden en meer dan 50% van het lumen opnieuw was vernauwd. Patiënten werden geëxcludeerd wanneer men niet in staat was om minimaal 10 meter te lopen tijdens de initiële loopbandtest. Door middel van een progressieve loopbandtest werden aan het begin en na 1, 3 en 6 maanden follow-up zowel de initiële claudicatio afstand als de absolute claudicatio afstand gemeten. Veranderingen in loopafstand werden berekend door middel van het gemiddelde percentage verandering. Van januari tot en met december 2005 werden 23 opeenvolgende patiënten met recidief klachten van claudicatio intermittens geïnccludeerd. Drie patiënten (13,0%) stopten met gesuperviseerde looptherapie na 1 tot 6 maanden. Bij 6 patiënten (26,1%) bleek de gesuperviseerde looptherapie onvoldoende de symptomen te verminderen en werd een vasculaire interventie verricht. Het gemiddelde toename percentage van de initiële claudicatio afstand bedroeg 316% na 3 maanden en 411% na 6 maanden follow-up. De stijging van de absolute claudicatio afstand na 3 en 6 maanden bedroeg respectievelijk 299% en 317%. Deze pilot studie toont dat patiënten met een eerdere vasculaire interventie en recidief klachten van claudicatio intermittens significant voordeel kunnen ondervinden van gesuperviseerde looptherapie. De loopafstanden toonden een grote significante toename over een periode van 6 maanden.

De aanwezigheid van PAV wordt vaak miskend door veel behandelaars en de patiënten zijn zich niet bewust van de mogelijke aanwezigheid hiervan, evenmin als van de gevaren van deze ziekte. Patiënten met PAV, onafhankelijk van de aan- of afwezigheid van klachten, hebben net zoveel recht op secundaire preventie om het risico op vasculaire mortaliteit te verminderen als patiënten met een cardiovasculaire aandoening. Het ontwikkelde klinisch voorspellende PREVALENT model biedt aan huisartsen de mogelijkheid om op een eenvoudige en effectieve manier een risicovolle populatie te screenen op PAV. Als belangrijkste conservatieve behandeling zou looptherapie voor alle patiënten met symptomatisch PAV beschikbaar moeten zijn in een gesuperviseerde, regionale vorm. Hiermee kunnen vele meer risicovolle interventies worden voorkomen.

List of Publications

Bendermacher BLW, Kruidenier LM, Teijink JAW. **Supervised exercise therapy for intermittent claudication in a community-based setting.** Chapter in "More vascular and endovascular challenges", Charing Cross 2007; accepted

Bendermacher BLW, Willigendael EM, Nicolaï SPA, Kruidenier LM, Welten RJThJ, Hendriks EJM, de Bie RA, Prins MH, Teijink JAW. **Supervised exercise therapy for intermittent claudication in a community-based setting is as effective as clinic-based.** J Vasc Surg 2007; accepted

Bendermacher BLW, Teijink JAW, Willigendael EM, Bartelink ML, Peters RJG, de Bie RA, Büller HR, Boiten J, Langenberg M, Prins MH. **A clinical prediction model for the presence of peripheral arterial disease – the benefit of screening before initiation of measurement of the ankle brachial index: observational study.** Vasc Med 2007; accepted

Willigendael EM, Bendermacher BLW, Nicolaï SPA, Teijink JAW. **Looptherapie volgens de landelijke richtlijn voor patiënten met perifeer arterieel vaatlijden: de noodzaak van scholing.** Ned T Fysiotherapie 2007;1: 10-14.

Bendermacher BLW, Teijink JAW, Willigendael EM, Bartelink ML, Büller HR, Peter RJG, Boiten J, Langenberg M, Prins MH. **Symptomatic peripheral arterial disease: the value of a validated questionnaire and a clinical decision rule.** Br J Gen Pract 2006;56:932-937.

Nicolai SPA, Bendermacher BLW, Willigendael EM, Schambergen T, Hendriks EJM, Teijink JAW. **State of the art. Claudicatio intermittens.** Ned T Fysiotherapie 2006;4:78-82.

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Kuiken BW, Willigendael EM, Bendermacher BLW, Teijink JAW. **Stoppen met roken via een RookStopPoli.** Vasculaire Geneeskunde 2005;1:23-25.

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Dankwoord

Toen ik met de wetenschap begon had ik nog geen idee dat dit echt tot een waar proefschrift zou leiden. Gelukkig waren er mensen om mij heen die hier wel van overtuigd waren. Zonder hulp van al deze mensen had ik dit nooit kunnen volbrengen.

Dr. Teijink, Joep, om met jou te beginnen. Toen jij een co-assistent zocht voor het bijhouden van een database over de EVAR procedures, dacht ik, ach, waarom niet. Niet wetende dat dit een cruciale beslissing was voor mijn verdere loopbaan. Jij had, meer dan ikzelf, het volste vertrouwen in mij dat ik een proefschrift zou kunnen schrijven. Jouw eindeloze energie was en is een zeer belangrijke drijfveer om mij alert en actief te houden. Dankzij jou heb ik de vrijheid gehad om mij op het wetenschappelijke gebied te kunnen ontwikkelen, waardoor ik het met veel plezier heb kunnen volhouden. *De nevenactiviteiten in de vorm van theatervoorstellingen en winterbijscholingen organiseren zorgden voor een aangename afwisselende samenwerking.*

En dan mijn promotor, **Prof. Prins, Martin**, de eerste professor bij wie ik thuis op bezoek ging. Mijn zenuwen bleken al snel ongegrond, want vanaf het begin waren het zeer warme, aangename en bovendien uitermate nuttige bezoeken. Onder het genot van liters thee en vele koekjes zorgden jouw analytische interpretaties en suggesties steeds weer voor een rustige basis om weer verder te kunnen. Joep en Martin, jullie zijn echt een ultiem duo om bij te mogen promoveren!

Dr. Bartelink, Marie-Louise, onze samenwerking was door de afstand met name een digitale en telefonische samenwerking, welke ik desondanks als enorm prettig heb ervaren. Jouw altijd weer verhelderende ideeën, alles relativerend naar de praktijk, zijn buitengewoon bepalend geweest in de resultaten van dit proefschrift.

Dr. Willigendael, Edith, alias Willi de eerste, mijn grote voorbeeld. De eerste promovenda van Joep Teijink, als eerste alleen in de torenflat, de eerste artsonderzoeker van het NPPAV, en ga zo maar door. Diep respect heb ik voor jou ontwikkeld, hoe jij voor mij de weg hebt vrij gemaakt. Nog steeds kan ik altijd bij jou terecht wanneer dat nodig is en ik ben dan ook erg trots dat je één van mijn paranimfen bent. *Ik verheug me nu al om weer met jou samen te mogen werken in het AZM volgend jaar!*

Als tweede artsonderzoeker van het NPPAV was ik in de luxe positie dat ik geadviseerd en ondersteund werd door vele prominente artsen vanuit de gehele vasculair geneeskundige hoek: **Prof. Büller, Harry, Prof. Peters, Ron, Prof. Moll, Frans, Prof. de Bie, Rob, dr. Boiten, Jelis en dr. Langenberg, Machteld**. Eenieder wil ik hartelijk danken voor de prettige besprekingen in den lande en vooral ook voor alle ideeën en commentaren die ik van jullie heb mogen ontvangen.

Promoveren in een perifeer ziekenhuis is niet geheel gebruikelijk. Toch stonden alle **chirurgen en arts-assistenten van de vakgroep heekunde in het Atrium mc** hier positief tegenover en hebben mij gedurende deze periode veel vrijheid, vertrouwen en steun gegeven. Bovendien ben ik enorm verheugd dat ik onder hun leiding zal worden opgeleid tot chirurg. In het bijzonder wil ik de vaatchirurgen **dr. Welten**, tevens opleider, en **dr. Bollen** bedanken voor hun ondersteuning en de nuttige en prikkelende discussies die de nieuwe ontwikkelingen en resultaten van dit onderzoek teweeg brachten. Arts-assistenten chirurgie, als vreemde eend in de bijt was ik toch onder jullie vleugels. Jullie zijn fantastische collega's, bedankt voor het begrip, zeker in de laatste maanden.

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Het opzetten van het NLTP was een fantastische uitdaging. Alle betrokken **fysiotherapeuten** wil ik hartelijk bedanken voor hun medewerking, uithoudingsvermogen en hun vertrouwen in mij en het NLTP. De geweldige resultaten zeggen genoeg over jullie geleverde arbeid. Hoewel de ontwikkeling van het elektronisch patiënten dossier nogal wat voeten in aarde heeft gehad, mag het resultaat er nu dan toch wezen, met name dankzij **Rob de Bie**. Rob, bedankt hiervoor. **Erik Hendriks**, van jou heb ik veel over fysiotherapeuten en looptherapie geleerd. Bedankt voor de prettige samenwerking, met name tijdens alle nascholingen die we reizend door het hele land hebben gegeven.

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Blanche Hamers, gelukkig wist jij me regelmatig achter mijn laptop vandaan te plukken om wat leuks te gaan doen. Deze momenten waren steeds weer verzekerd van een onvoorspelbare, doch geweldige en onvergetelijke afloop. Je bent een fantastische vriendin en ik hoop nog heel veel van deze momenten met jou te beleven. Ik ben ontzettend blij dat jij één van mijn paranymfen bent.

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Bianca Bendermacher werd geboren op 29 september 1976 in Heerlen. Na het eindexamen atheneum in 1995 aan het Bernardinus College te Heerlen kon zij in 1997, na een derde loting in het kader van de numerus fixus, starten met de studie geneeskunde aan de Universiteit Maastricht.

Tijdens haar co-schap heelkunde werd de basis gelegd die uiteindelijk leidde tot dit proefschrift. Na haar artsexamen in 2003 kon zij zich voltijds gaan bezighouden met haar promotieonderzoek in het Atrium Medisch Centrum te Heerlen onder leiding van professor dr. Martin Prins en dr. Joep Teijink. Dit onderzoek werd mede geïnitieerd door het Nederlands Platform Perifeer Arterieel Vaatlijden (NPPAV). Naast haar onderzoek schreef zij een ZonMW aanvraag betreffende een multicenter studie naar de kosteneffectiviteit van gesuperviseerde looptherapie vergeleken met niet-gesuperviseerde looptherapie. Bij deze studie zijn momenteel 12 Nederlandse centra betrokken en zal in 2008 worden afgerond.

Op 1 juli 2006 is zij gestart met de opleiding tot algemeen chirurg in het Atrium Medisch Centrum in Heerlen (opleider: dr. R.J.Th.J. Welten).