The impact of exercise capacity in the atherosclerotic patient; Keep on walking!

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CONTENTS

Introduction

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PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease (PAD) is a manifestation of systemic arteriosclerosis [1-6]. It is a common disease affecting millions of people. Depending on the age of the investigated population prevalences between 4% to 29% has been reported [1, 7]. It is alarming that the prevalence is expected to rise in the following decades due to the aging of the western population and the increase of risk factors such as diabetes mellitus, obesity and lack of exercise [1, 6, 7]. Patients with PAD are of an increased risk of cardiovascular events and mortality [4, 8, 9]. In addition, they may also experience significant limitations in their physical functioning and impairment in their quality of life [3, 10-18]. It is important to diagnose patients with PAD early in the course of the disease to provide them optimal treatment as soon as possible in attempting to lower the complication rates, improve morbidity, mortality and subsequent their quality of life. However, symptoms of PAD are diverse [6, 19, 20]. The classical symptoms are intermittent claudication consisted of calf pain provoked by walking and declining at rest [19]. Earlier investigations, on the other hand, have demonstrated a large range of symptoms ranging from no pain at all till pain at rest [3, 19, 21-24]. A major problem is that between 20% till 50% of the patients are asymptomatic [2-4, 6, 20, 23, 25, 26]. Commonly, to identify patients with PAD the resting ankle brachial index (ABI) is used. This is the ratio between the ankle's systolic blood pressure, measured at the dorsalis pedis or posterial tibial arterie using a Doppler ultrasonic instrument, and the systolic blood pressure at the arm [3-5, 27]. An ABI below 0.90 is associated with angiographic stenosis of more than 50% [4]. According to the guidelines a resting ABI of < 0.90 is defined as PAD. Several studies have found that an ABI of < 0.90 is associated with an increased risk of cardiovascular diseases and mortality. Moreover it can also be used for prognostic risk stratification [1, 9, 28].

TREADMILL EXERCISE TEST AND EXERCISE ANKLE BRACHIAL INDEX

A treadmill exercise test is often used to diagnose or to evaluate PAD. These exercise tests are mostly performed in a vascular laboratory and supervised by specially trained personnel. Using these exercise tests patients who will otherwise stayed unnoticed may be identified and treated accordingly. However, in contrast to the value of the exercise test in cardiac patients, the value of exercise tests in patients suspected for PAD is still unclear and hardly investigated. One of the parameters measured at these tests is the exercise ABI. More than 30% of the patients who have according to the guidelines a normal resting ABI, showed to have an ABI < 0.90 after a treadmill exercise test [29]. In **Chapter 2** we investigate which patient characteristics are associated with an abnormal exercise ABI. In addition we explore the prognostic value of the exercise ABI.

ABNORMAL BLOOD PRESSURE RESPONSE

Exercise tests provide a large amount of other clinical variables which might be important risk factors for cardiovascular morbidity and mortality. One of these parameters is the blood pressure response at exercise. During dynamic exercise a rise in the systolic blood pressure with no change or a slightly decrease in the diastolic blood pressure is a normal blood pressure response [30]. However, some patients show a decline in systolic blood pressure during an exercise test, known as a hypotensive blood pressure response, which is thought to be a sign of severe coronary artery disease [31-34]. One other less well known exercise response is the hypertensive blood pressure response. These phenomenons are mostly investigated in cardiac patients, but hardly in patients with PAD [31-34]. Therefore we looked into these associations in patients with PAD, which are displayed in **chapter 3 and 4**. In **chapter 5** we investigate if these abnormal blood pressure responses were also related with an increased risk of complications at major elective vascular surgery.

WALKING DISTANCE

A further measured parameter at the exercise test is the total walking distance. Patients with PAD experience an impaired peripheral circulation, which causes significant limitation in their physical functioning and walking in particular [4, 20, 35-39]. However, in contrast to the clinical value of the resting ABI, the clinical value of the walking distance is still unclear. Therefore, we investigated the relationship between the walking distance and cardiovascular morbidity and mortality in both patients with an ABI < 0.90 and ≥ 0.90 (**chapter 6**). Besides we also wanted to know if the walking distance has effects on their quality of life (**chapter 7**). In addition, multiple exercise tests could also be an important tool to assess the progression of the disease. Therefore we looked into the association between the decline in walking distance and mortality risk (**chapter 8**).

EXERCISE TEST PARAMETERS

Finally, we were interested in the effect of the combination of the different exercise test parameters together on long-term outcome. Therefore, we investigated the combination of the different exercise test parameters together (resting and exercise ABI, walking distance and blood pressure response) in relation with cardiovascular mortality (**chapter 9**). In the last chapter we give an overview of the literature and most of the study results (**chapter 10**).

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Exercise ankle brachial index

2

Exercise ankle brachial index adds important prognostic information on long-term out-come only in patients with a normal resting ankle brachial index

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Arthrosclerosis: in press

ABSTRACT

Background: The clinical value of exercise ankle brachial index (ABI) is still unclear, especially in patients with normal resting ABI.

Method: 2164 patients performed a single-stage treadmill exercise test to diagnose or evaluate PAD. The population was divided into two groups: a normal resting ABI (resting ABI ≥ 0.90) and PAD (resting ABI < 0.90). Patients with a normal resting ABI were divided into 4 exercise ABI groups: exercise ABI < 0.90, 0.90-0.99, 1.00-1.09 and 1.10-1.29 (reference).

Results: Mean follow-up was 5 years. Exercise ABI added significant prognostic information on all cause long-term mortality only in patients with normal resting ABI (p-value 0.014, HR 0.99 95% CI (0.98-0.99)), not in patients with PAD. Fifty years or older (OR 2.93 95% CI (1.65 - 5.20)) and resting systolic blood pressure > 140mmHg (OR 2.18 95% CI (1.35 - 3.55)) were associated with an abnormal exercise ABI in patients with a normal resting ABI. Mortality rate increased when the exercise ABI became worse (p trend 0.0001) with a 2.5 fold increase mortality risk in patients with a normal resting ABI but exercise ABI <0.90 (HR 2.56, 95% CI (1.11 - 5.91)).

Conclusion: In patients with a normal resting ABI, treadmill exercise ABI added important prognostic information on long-term mortality. Based on our results we recommend that at least all patients suspected for PAD, with a resting ABI ≥ 0.90, who are 50 years or older and having hypertension should undergo treadmill exercise testing.

INTRODUCTION

Peripheral arterial disease (PAD) is a manifestation of systemic arteriosclerosis [1] Commonly, the ankle brachial index (ABI) is used to diagnose PAD [2]. According to the guidelines, a resting ABI < 0.90 is defined as PAD, which is related to a higher cardiovascular morbidity and mortality [2-4]. According to the current definitions, patients with ABI ≥ 0.90 are now defined as having a normal ABI [2]. However, recent publications showed that resting ABI values between 0.90 - 1.10 are already associated with a higher mortality and impairment in physical performance, compared to patients with a resting ABI between 1.10-1.30 [5-8]. One study observed that 31% of the patients with a resting ABI ≥ 0.90 showed to have a ABI below the 0.90 after a treadmill exercise test [9]. However, it is still not completely clear in which patients the exercise ABI adds additional prognostic information. Therefore, we investigated the association between exercise ABI and long-term out-come in patients with normal resting ABI and PAD.

MATERIALS AND METHODS

Study Population

Our study population consisted of 2164 consecutive patients, who were referred by general practitioners or physicians to the vascular laboratory of the Erasmus Medical Centre, Rotterdam, the Netherlands, for a single-stage treadmill exercise test, between 1993 and 2006. Patients were referred by physicians to diagnose PAD, based on their presenting symptoms, or to evaluate their PAD. Excluded were patients who were unable to perform the treadmill exercise test. Also patients with a resting ABI > 1.30 (17 patients) were excluded from the analyses.

Single-stage exercise test

Specialised trained personnel supervised the exercise tests, using a prescribed protocol. Patients were asked not to smoke before the test. The systolic blood pressure was measured with a blood pressure device (Maxi stable 3, presso stabl; Welch Allyn Inc, Skaneateles Falls, New York, USA) with 40% of the limb contour at both left and right arms in supine position after 15 minutes rest. In addition, the blood pressure at the anterior tibial and posterial tibial arteries was measured at both sides, using a Doppler ultrasonic instrument with a 8-MHZ vascular probe (Imexdop CT+ vascular Doppler; Miami Medical, GlenAllen, Va). After these measurements all patients were asked to walk on a treadmill with a speed of 4 km/h for a maximum of 5 minutes. No inclining plane or graded inclines were used. During the walking test patients were ask to tell the personnel when they started to feel pain in the legs. Patients were encouraged to finish the whole test. Immediately

after the exercise the systolic blood pressure at the arm, as well as at the anterior tibial or posterial tibial artery, depending which one was highest at rest, were measured in supine position. ABI at rest and after the exercise test were calculated by dividing the systolic blood pressure at the dorsalis pedis or posterial tibial arteries, depending which one was the highest, by the highest systolic blood pressure at the arm. For the resting ABI the interobserver and intraobserver agreement was 97% and 98%, and for the exercise ABI 96% and 97%, as described previously [10]. All variables were incorporated in a computerised hospital database.

Covariate assessment

From the medical records, the following baseline characteristics were collected: age, gender, current smoking, diabetes mellitus, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, renal dysfunction, history of congestive heart failure, history of cardiac disease consisted of angina pectoris, myocardial infarction or coronary artery revascularisation. The following definitions were used for the different covariates. Diabetes mellitus was documented when patients presented with the diagnosis, made by the referred physician, required anti-diabetic medication, having a fasting glucose level ≥ 126mg/dl, a glucose level of ≥ 200mg/dl after a oral glucose tolerance test or plasma non-fasting glucose levels of ≥ 200mg/dl [11, 12]. Hypertension was recorded if a patient had a blood pressure higher > 140/90mmHg or treated with antihypertensive medication. Chronic obstructive pulmonary disease was classified as a history of chronic obstructive pulmonary disease or pulmonary medication use. Hypercholesterolemia was noted when patients presented with the diagnosis, made by the referred physician, received lipid-lowering medication or a plasma cholesterol level of 212mg/dl or more. Renal dysfunction was defined as having a serum creatinine level of ≥2.0 mg/dl or receiving dialyses.

Follow-up

The follow-up vital status, which was obtained by reviewing the civil registries, was completed for 99.4%. The survival status of six patients who had moved abroad could not be retrieved, and the last available follow-up data were used. The cause of death was obtained from the Central Bureau of Statistics or from medical records. Cardiac death was defined as death of cardiac origin caused by myocardial infarction, cardiac arrhythmias or congestive heart failure.

Statistical methods

The study population was divided into patients with PAD, defined as resting ABI <0.90, and patients with normal resting ABI, defined as resting ABI ≥ 0.90. To identify differences in baseline characteristics between patients with PAD and patients with normal resting ABI, student's t- tests for continuous variables and chi-square tests for categorical variables

were used. With adjustments for baseline characteristics (age, gender, current smoking, diabetes mellitus, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, renal dysfunction, history of congestive heart failure, history of cardiac disease consisted of angina pectoris, myocardial infarction or coronary artery revascularisation and systolic resting blood pressure), multivariate Cox proportional hazard regression analyses with the enter method, were used to investigate the additional value of exercise ABI on all cause long-term mortality. To confirm the proportional hazard assumption the proportionality of hazards was tested graphically based on visual inspection of log-log survival curves. Included variables in the baseline model were age, gender, current smoking, diabetes mellitus, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, renal dysfunction, history of congestive heart failure, history of cardiac disease consisted of angina pectoris, myocardial infarction or coronary artery revascularisation, systolic resting blood pressure and resting ABI. Logistic regression analyses with the forward method were used to investigate which baseline characteristics were associated with an abnormal exercise ABI in patients with a normal ABI. Logistic regression analyses and receiver operating characteristic (ROC) curves were made to investigate which cut-off value for age was associated with the abnormal exercise ABI. Cox proportional hazard ratio's (HR) with 95% confidence interval (95% CI) were calculated to define the relationship between the five patient groups and all cause long-term mortality. All analyses were repeated for cardiac death. For all tests significance was defined as a P-value of ≤ .05. Analyses were performed in SPSS 15 for windows.

RESULTS

The mean follow-up period was 5 years (range from 0.5 year to 14 years). Baseline characteristics of patient with PAD and normal resting ABI are shown in table 1.

The log-log survival curves to test the proportionality of hazards did not show interactions with time. After adjustment for all known baseline characteristics in patients with a normal resting ABI, exercise ABI added significant information to the other known risk factors for all cause long-term mortality (Chi-square 6.023, p-value 0.014). When both resting ABI and exercise ABI together were added into the model, the multivariate analyses showed that exercise ABI (HR 0.988, 95% CI (0.978-0.997) p-value 0.012) was related to all cause long-term mortality than the resting ABI (HR 0.981 (0.956-1.007)) p-value 0.15).

This indicates that in patients with a normal resting ABI, not the resting ABI but the exercise ABI is the important prognostic factor of long-term out-come.

In contrast, in patients with PAD the resting ABI (HR 0.991 95% CI (0.983-0.991) p-value 0.019) was strongly related to all cause long-term mortality, but exercise ABI did not

Table 1. Baseline characteristics in patients with PAD and patients with normal resting ABI.

Characteristics	*Resting ABI < 0.90 (PAD) n=1342*	*Resting ABI ≥ 0.90 (Normal Resting ABI) n= 822*	*p-value*
Age (years)	64 ± 11	60 ± 13	0.0001
Body mass index (kg/m^2)	26 ± 8	27 ± 5	0.2
Male (%)	947 (71)	507 (61)	0.0001
COPD (%)	174 (13)	104 (13)	0.8
Hypertension (%)	546 (41)	249 (31)	0.0001
Diabetes mellitus (%)	259 (20)	150 (18)	0.5
Current smoking (%)	462 (35)	235 (29)	0.04
Hypercholesterolemia (%)	498 (38)	208 (26)	0.7
Renal failure (%)	80 (6)	61 (8)	0.2
History of cardiac disease (%)	457 (34)	266 (33)	0.4
History of heart failure (%)	86 (7)	44 (5)	0.3

Values are means with standard deviations or numbers with percentages.

add addition prognostic information (Chi-square 0.049, p-value 0.83 HR 1.001 95%CI (0.995 - 1.007)).

In order to investigate which baseline characteristics were associated with an abnormal exercise ABI in patients with a normal ABI logistic regression method was used. Age ≥ 50 years and resting systolic blood pressure > 140mmHg were associated with exercise ABI < 1.10 (Table 2). Age ≥ 50 years, current smoking, hypercholesterolemia and a resting systolic blood pressure > 140 mmHg were associated with an exercise ABI < 0.90 (Table 2). As exercise ABI added additional information on all cause long-term mortality only in patients with normal resting ABI, this patient group was divided into four exercise ABI groups: exercise ABI < 0.90, 0.90-0.99, 1.00-1.09 and 1.10-1.29 (reference group). Of the patients with a resting ABI > 0.90, only 14% had an exercise ABI between 1.10-1.30 and

Table 2 Logistic regression analyses to investigate the association between baseline characteristics and an abnormal exercise ankle brachial index in patients with normal resting ankle brachial index.

	Normal resting ABI + Exercise ABI 1.10-1.29 (reference)	*Normal resting ABI + Exercise ABI <1.10 (OR ,95% CI)*	*Normal resting ABI Exercise ABI < 0.90 (OR ,95% CI)*
Age: ≥ 50 years	1	**1.76 (1.12-2.76)**	**2.93 (1.65-5.20)**
Resting systolic blood pressure >140	1	**1.64 (1.06-2.54)**	**2.18 (1.35-3.55)**
Current Smoking	1	-	**1.76 (1.03 - 3.06)**
Hypercholesterolemia	1	-	**1.62 (1.00-2.65)**

Bold characters are significant values with p-value ≤ 0.05

Table 3. Numbers and percentage of patients with a resting ABI ≥ 0.90 and different exercise ABI results.

	Exercise ABI 1.10-1.30	*Exercise ABI 1.00-1.09*	*Exercise ABI 0.90-0.99*	*Exercise ABI < 0.90*	*Total*
Resting ABI 1.10-1.30	51 (47%)	32 (30%)	13 (12%)	12 (11%)	108
Resting ABI 1.00-1.09	63 (13%)	175 (37%)	126 (27%)	110 (23%)	474
Resting ABI 0.90-0.99	5 (2%)	25 (10%)	48 (20%)	162 (68%)	240
Total	119 (14%)	232 (28%)	187 (23%)	284 (35%)	822

35% showed an exercise ABI < 0.90 (Table 3). Striking was that 11% of the patients with a completely normal resting ABI (1.10-1.30) had an exercise ABI < 0.90 (Table 3).

Figure 1 shows the mortality rate in the four exercise ABI group and in patients with PAD. The mortality rate significantly increased when the exercise ABI became worse (P trend 0.0001).

After adjustments for baseline characteristics, the worse the exercise ABI was, the higher the risk of all cause long-term mortality became, with the highest risk of long-term mortality in patients with normal resting , but an exercise ABI <0.90 (HR 2.56, 95% CI(1.11 - 5.91), Table 4). Additional adjustment for baseline medication use (statin, ace-inhibitors and beta-blocker) did not influence the results. Comparable results were seen when all analyses were repeated for cardiac death.

Figure 1. Percentage of long-term mortality in the four exercise ABI groups and patients with PAD.

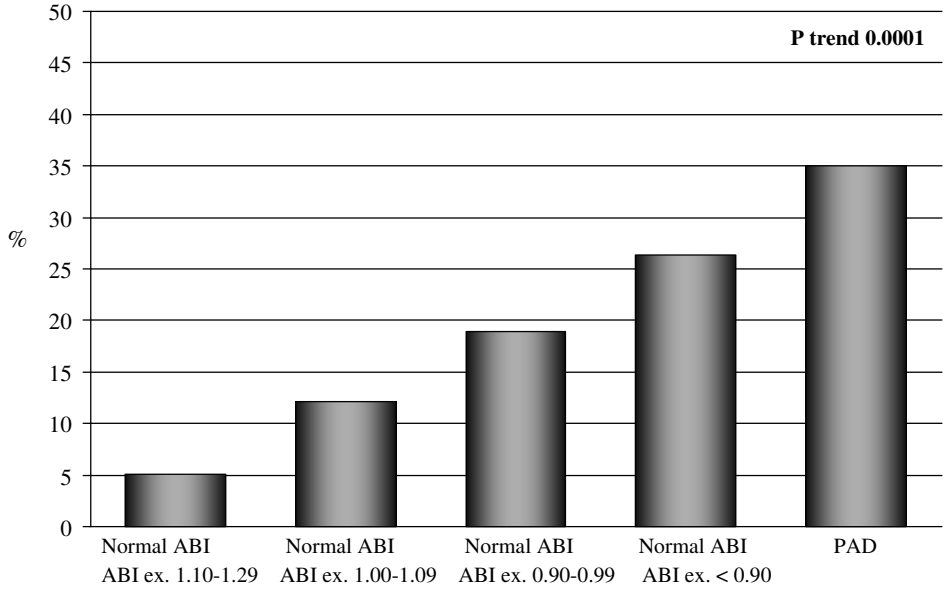

Table 4 Hazard ratio's and 95% confidence intervals on all cause long-term mortality in four exercise ABI groups and patients with PAD.

All cause long-term mortality	*Model I (HR ,95% CI)*		*Model II (HR ,95% CI)*	
Normal Resting ABI				
Exercise ABI 1.10-1.29	Ref		Ref	
Exercise ABI 1.00-1.09	1.63	(0.67 - 3.94)	1.31	(0.54 - 3.17)
Exercise ABI 0.90-0.99	2.18	(0.92 - 5.19)	1.95	(0.82 - 4.64)
Exercise ABI < 0.90	**2.95**	**(1.28 - 6.78)**	**2.56**	**(1.11 - 5.91)**
PAD	**3.18**	**(1.42 - 7.14)**	**2.73**	**(1.22 - 6.14)**

Model I = age and gender
Model II = Model I + current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, renal failure and resting systolic blood pressure
Bold characters are significant values with p-value ≤ 0.05

DISCUSSION

In the present study we showed that in patients with a normal resting ABI, exercise ABI added significant information on long-term mortality. In these patients the exercise ABI was more important related to long-term mortality than the resting ABI. Especially patients with still a normal resting ABI but who were > 50 years and having hypertension were associated with an abnormal exercise test. With worsening of the exercise ABI, mortality risk increased. In contrast, in patients with PAD (resting ABI < 0.90) exercise ABI did not add prognostic information.

PAD is a manifestation of systemic arteriosclerosis, affecting millions of people with prevalence's between 4 to 29% and is expected to rise in the following decades [1]. ABI is used to assess peripheral arterial disease [13]. According to the guidelines, a resting ABI < 0.90 is defined as PAD, which is related to a higher cardiovascular morbidity and mortality [2-4, 14]. However, the ankle systolic blood pressure is normally higher than the systolic blood pressure at the arm [15]. Therefore, ABI of less than 1.10 should be considered as abnormal. Recent publications indeed showed that resting ABI between 0.90 - 1.10 was associated with subclinical atherosclerosis of the coronary and carotid arterial beds, higher mortality and impairment in physical performance compared to patients with ABI between 1.10-1.30 [5-8, 16-18]. However, in the present study it was observed that in this patient category the exercise ABI was more important than the resting ABI. More than one-third of the patients with normal resting ABI (ABI ≥ 0.90) demonstrated an ABI <0.90 after a treadmill exercise test and still 11% of the patients with a completely normal resting ABI (ABI 1.10-1.30)

had an exercise ABI < 0.90. A previous study from our study group already showed that exercise ABI could be of prognostic value and showed that a reduction of the exercise ABI compared to the resting ABI was associated with higher mortality [10]. However, no investigation was performed in which patient group the exercise ABI added additional information over the resting ABI and in which group it did not. Furthermore, no other studies have investigated which baseline characterises were associated with an abnormal exercise ABI.

Untill to day, the clinical value of exercise test in patients suspected of PAD is still not completely clear. In the inter-society consensus for management of PAD and in a previous study it was suggested that a resting ABI < 0.90 was enough to diagnose PAD and no exercise test was needed [19, 20]. The present study confirmed this recommendation. However, it was also recommend that in patients with a resting ABI between 0.90-1.30 and claudication symptoms, an exercise test can be considered [19, 20]. Our study showed that in this patient group exercise tests will be of important clinical value. From different other studies it is known that symptoms in patients with PAD vary between the typical claudication symptoms till no symptoms at all [13, 14, 21-24]. Therefore, clinical symptoms will not be helpful to decide which patients should undergo exercise testing. We observed that patients > 50 years and hypertension were related with an abnormal exercise test, especially in combination with hypercholesterolemia and smoking. As a consequence, we suggest strongly that all patients with a resting ABI ≥ 0.90, who are >50 years and having a systolic blood pressure of >140mmHg all needs to undergo a treadmill exercise testing.

Despite the large study population and long follow-up, there are some limitations. The study is performed in a tertiary hospital and it is unclear whether these findings are generalizable for the general practitioners practise. All patients must have had some symptoms, because all patients were referred to our hospital by general practitioners or other physicians. Therefore, it is unlikely that our data contained completely asymptomatic patients. Additional researches at general practitioners are needed to answer this question.

CONCLUSION

In patients with a normal resting ABI, treadmill exercise ABI added important prognostic information on long-term out-come. Based on our results we strongly recommend that at least all patients suspected for PAD, with a resting ABI ≥ 0.90, who are 50 years or older and having hypertension should undergo treadmill exercise testing.

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Abnormal blood pressure response

3

The usefulness of hypertensive blood pressure response during a single-stage exercise test to predict long-term outcome in patients with peripheral arterial disease

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ABSTRACT

The prognostic value of a hypertensive blood pressure (BP) response is still unclear. Therefore, the prognostic value of a hypertensive BP response in patients during a single-stage exercise tests for peripheral arterial disease (PAD) on long-term mortality and major adverse cerebrovascular and cardiac events (MACCE) was investigated. In addition, effects of statin, beta-blocker and aspirin use in patients with known or suspected PAD were studied. A total of 2109 patients were enrolled in an observational prospective study between 1993 and 2005. Hypertensive BP response was defined as an increase in systolic BP ≥ 55mmHg (95^{th} percentile within our population), after a single-stage treadmill exercise test. The outcome was obtained by the civil registries and a questionnaire about cardiac events was sent to all survivals. A hypertensive BP response was associated with an increased risk of long-term mortality (hazard ratio (HR) 1.42, 95% confidence interval (CI) [1.12-1.80]) and MACCE (HR 1.47 [1.09-1.97]). After adjustments for clinical risk factors and propensity score, baseline statin use was associated with a reduced risk of long-term mortality (HR 0.59, 95% CI [0.44-0.79]) and statin, beta-blocker and aspirin use were associated with a reduced risk of MACCE (HR 0.59, 95%CI [0.43-0.81], HR 0.75, 95%CI [0.60-0.95] and HR 0.73, 95%CI [0.57-0.92], respectively). In conclusion, hypertensive BP response at exercise in patients with known or suspected PAD is an important independent risk factor for all cause long-term mortality and MACCE, whereas statin, beta-blocker and aspirin use were associated with an improved outcome.

INTRODUCTION

Exercise tests are widely used to diagnose cardiovascular diseases. A number of patients develop a hypertensive blood pressure (BP) response during an exercise test. However, the clinical value of this hypertensive BP response during exercise is still unclear. A few studies have investigated the relations among hypertensive BP response, cardiovascular diseases and mortality, but mostly preformed in healthy populations [1-12]. In addition, the effects of statin, beta-blocker and aspirin use on mortality risk in patients with peripheral arterial disease (PAD) have been investigated previously in a number of studies, but have not yet been discussed in patients with hypertensive BP response [13-20]. To bridge these knowledge gaps, we performed an observational study to assess the predictive value of hypertensive BP response after a single-stage exercise test on long-term all cause mortality, major adverse cerebrovascular and cardiac events (MACCE) and the effects of statin, beta-blocker and aspirin use in patients with known or suspected PAD.

METHODS

Our study population consisted of 2109 patients referred to the Erasmus Medical Centre, Rotterdam, the Netherlands, from July 1993 to December 2005 with a history of intermittent claudication, pain in the legs, or other symptoms of arterial insufficiency such as ulcerations, for a single-stage treadmill walking test to diagnose or evaluate PAD.
Specialised trained personnel executed the exercise tests, using a prescribed protocol. The systolic BP was measured with an blood pressure device (Maxi stable 3, presso stabl; Welch Allyn Inc, Skaneateles Falls, New York, USA) in both left and right arms in the supine position after 15 minutes of rest. In addition, the BP at the dorsalis pedis and posterial tibial arteries were measured on both sides, using an imexdop CT+ vascular Doppler (Imexdop CT+ vascular Doppler; Miami Medical, GlenAllen, Va). After these measurements all patients were asked to walk on a treadmill with a speed of 4 km/h for a maximum of 5 minutes. No inclining plane or graded inclines were used. During the walking test patients were ask to inform the personnel when pain in the legs occurred. Patients were encouraged to finish the entire test. The total walking time and distance were recorded. Immediately after the exercise the systolic BP at the arm and dorsalis pedis or posterial tibial artery, depending which one was highest at rest, were measured in supine position. All variables were incorporated in a computerised hospital database.
We identified the 95th percentile of the increase in systolic BP, the difference between the highest measured exercise systolic BP and the highest measured resting systolic BP, in patients within our population without hypertension, chronic obstructive pulmonary disease, cardiovascular history or renal dysfunction. This was 55 mmHg. Next, we defined

hypertensive BP response as an increase in systolic BP ≥ 55mmHg at exercise. Using these criteria, 180 patients (9%) developed a hypertensive BP response at the exercise test. Patients with an increase in systolic BP < 55mmHg were defined as having a normal BP response. Patients who experienced a decrease in systolic BP after exercise compared with the resting systolic BP were excluded from analyses. Ankle brachial index at rest and after the exercise test were calculated by dividing the systolic BP at the dorsalis pedis or posterial tibial arteries, depending which one was the highest, by the highest systolic BP at the arm.

From the medical records, baseline characteristics of age, gender, current smoking, diabetes mellitus, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, renal dysfunction, angina pectoris, history of heart failure, previous myocardial infarction, coronary artery revascularisation and baseline use of statin, beta-blocker or aspirin were gathered. The 12-lead electrocardiography was screened for abnormalities. The following definitions were used for the different covariates. Diabetes mellitus was documented when patients presented with the diagnosis made by the referred physician or required antidiabetic medication. Hypertension was recorded if a patient had a BP > 140/90mmHg or was treated with antihypertensive medication. Chronic obstructive pulmonary disease was classified as a history of chronic obstructive pulmonary disease or pulmonary medication use. Hypercholesterolemia was noted when patients presented with the diagnosis made by the referred physician or received lipid-lowering medication. Renal dysfunction was defined as having a serum creatinine level of ≥2.0 mg/dl or receiving dialyses.

Follow-up for vital status, which was obtained by reviewing the civil registries, was completed for 99.4%. The survival status of 6 patients who had moved abroad could not be retrieved, and the last available follow-up data were used. Causes of death were obtained from the civil registries or medical records. Of 62 patients (10%) no course of death could be traced. Additionally, for all 1497 survivors, a self-reporting questionnaire about cardiac events and current medication use were sent, and 73% returned the questionnaire.

To identify differences in baseline characteristics and exercise results between patients with a hypertensive BP response and those with a normal BP response student's t- tests for continuous variables were used and chi-square tests for categorical variables. Cox proportional hazard ratio's (HR) with 95% confidence interval (CI) with adjustments for potential clinical risk factors (age, gender, current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, renal failure, resting systolic BP and resting ankle brachial index) were calculated to define the relationship between hypertensive BP response, long-term mortality, MACCE (hospital admission for angina pectoris, non-fatal myocardial infarction diagnosed in a hospital and defined as acute coronary syndrome with rise in troponin or rapid rise and fall of CK-MB, or pathologic findings of acute myocardial infarction, or coronary artery bypass grafting or percutane

transluminale coronair angioplastiek)) and statin, beta-blocker or aspirin use [21]. Additional adjustments were made using propensity scores, a probability of being treated, calculated on the individual's covariates, to reduce the effects of selection bias [22]. The Kaplan Meier method with log-rank tests was used to compare survival of both groups and the effects of statins, beta-blockers and aspirin use on the survival. For all test significance was defined as p-value of ≤ 0.05. Analyses were performed in SPSS 14 for windows.

RESULTS

Mean age was 63 years, with 67% men. Patients with hypertensive BP response were significantly older and had more often hypertension at baseline compared with patients with a normal BP response (Table 1). Before the single-stage exercise test, patients with hypertensive BP response had a significant higher resting systolic BP than patients with normal BP response and a significant lower resting and exercise ankle brachial index (Table 2).

Table 1. Baseline characteristics in patients with hypertensive and normal blood pressure response.

Characteristics	Hypertensive blood pressure response (n=180)	Normal blood pressure response (n=1929)	p-value
Male	133 (74%)	1289 (67%)	0.052
Age (years)	**66 ± 8.6**	**62 ± 12.2**	**0.001**
Body mass index (kg/m^2)	27 ± 6.4	26 ± 6.9	0.28
Chronic obstructive pulmonary disease	28 (16%)	248 (13%)	0.30
Hypertension	**79 (44%)**	**694 (36%)**	**0.04**
Diabetes mellitus	39 (22%)	321 (17%)	0.09
Current smoking	55 (31%)	617 (32%)	0.67
Hypercholesterolemia	47 (26%)	489 (26%)	0.85
Renal dysfunction	12 (7%)	127 (7%)	0.98
Angina pectoris	25 (14%)	318 (17%)	0.34
Previous myocardial infarction	40 (22%)	405 (21%)	0.74
Coronary artery bypass grafting	28 (16(%)	224 (12%)	0.13
Percutaneous coronary intervention	14 (8(%)	145 (8%)	0.93
Heart failure	9 (5(%)	119 (6%)	0.51
Electrocardiography abnormalities	63 (38%)	540 (31%)	0.08
Statin use	60 (34(%)	608 (32%)	0.64
Beta-blocker use	53 (30%)	608 (32%)	0.58
Aspirin use	51 (29%)	533 (28%)	0.70

Values are means with standard deviations or numbers with percentages.

Table 2. Results of exercise test in patients with hypertensive and normal blood pressure response.

Variable	Hypertensive blood pressure response (n=180)	Normal blood pressure response (n=1929)	p-value
Systolic blood pressure at rest (mmHg)	**157 ±24**	**150 ±26**	**0.001**
Ankle brachial index at rest (mmHg)	**71 ±24**	**77 ±25**	**0.001**
Total walking distance (meters)	226 ±88	227 ±99	0.90
Systolic blood pressure after exercise (mmHg)	**222 ±27**	**173 ±31**	**0.001**
Ankle brachial index after exercise (mmHg)	**41 ±27**	**60 ±32**	**0.001**

Values are means with standard deviations.

The mean follow-up period was 5.0 years (range 0.5 to 14 years). During the follow-up period, 27% died in the normal BP response group and 44% in the hypertensive BP response group. MACCE occurred in 30% in the normal BP response group and 45% in the hypertensive BP response group.

Patients with a hypertensive BP response had an increased risk of long-term all cause mortality and MACCE compared with patients with normal BP response, independent of other clinical variables (Table 3).

Cumulative survival of long-term all cause mortality and MACCE in patients with a hypertensive BP response was significantly worse compared with patients with a normal BP response (p-value 0.0001 and 0.0001, respectively; Figure 1).

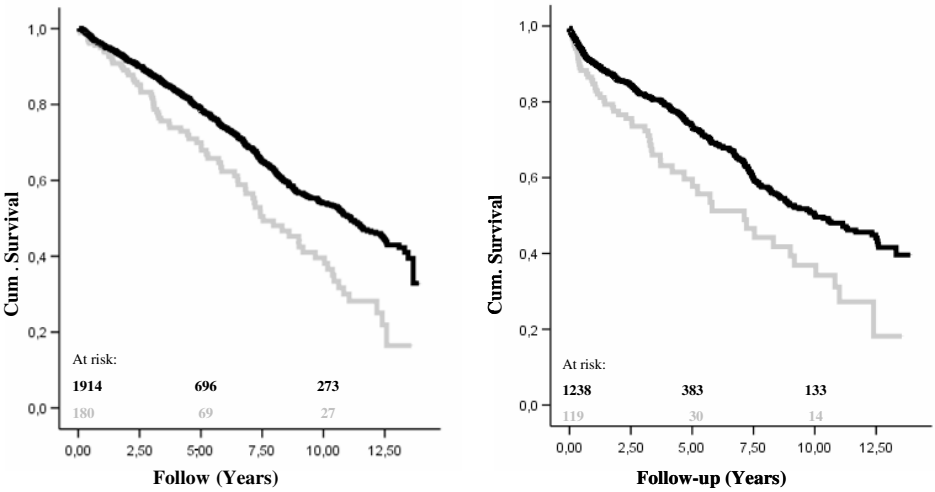
Baseline statin use was associated with a reduced risk in all cause long-term mortality independent of other clinical variables and independent of the propensity score (HR 0.59 95%CI [0.44-0.79]; Figure 2). Beta-blocker use was borderline significant (HR 0.88 95%CI [0.72-1.08]) and aspirin use was not significantly related with a reduced risk in all cause long-term mortality (HR 0.91 95%CI [0.74-1.11]). However, statin, beta-blocker and

Table 3. Hazard ratios (HR) with 95% confidence interval (CI) for long-term all cause mortality and major adverse cerebrovascular and cardiac events (MACCE) in patients with hypertensive compared with normal blood pressure (BP) response.

Model	I HR (95%CI)	II HR (95%CI)	III HR (95%CI)	IV HR (95%CI)
Normal BP response	1	1	1	1
Hypertensive BP response				
All cause mortality	**1.39 (1.10-1.76)**	**1.45 (1.14-1.84)**	**1.44 (1.14-1.83)**	**1.42 (1.12-1.80)**
MACCE	**1.51 (1.13-2.01)**	**1.54 (1.15-2.10)**	**1.52 (1.13-2.04)**	**1.47 (1.09-1.97)**

Model I = age and gender
Model II = Model I + current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases and renal failure
Model III = Model II + SBP at rest
Model IV = Model II + SBP at rest + ABI at rest

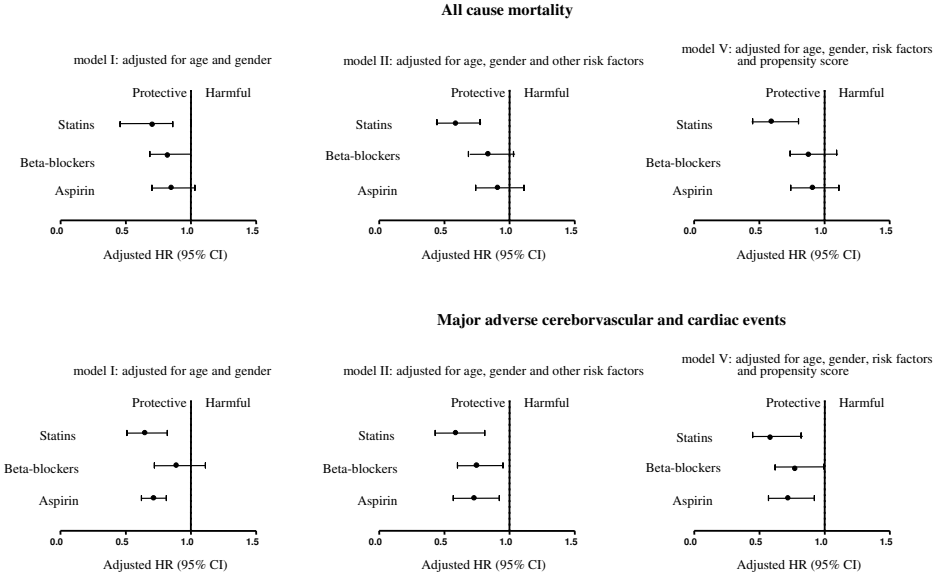
Figure 1. Survival curves for normal and hypertensive blood pressure response during exercise for long-term all cause mortality and major adverse cerebrovascular and cardiac events.



1a. All cause long term mortality
Normal blood pressure response
Hypertensive blood pressure response

1b. MACCE
Normal blood pressure response
Hypertensive blood pressure response

Figure 2. The effect of beta-blocker, statin and aspirin use in patients with hypertensive blood pressure response for long-term all cause mortality and major adverse cerebrovascular and cardiac events.

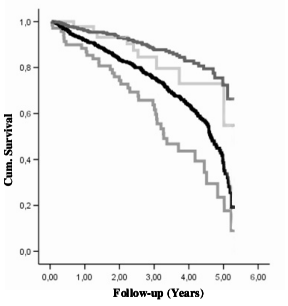


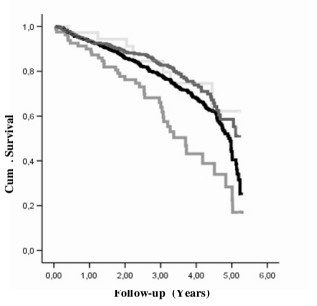
aspirin use were all significantly associated with a decreased risk of MACCE independent of other clinical variables (HR 0.59, 95%CI [0.43-0.81], HR 0.75, 95%CI [0.60-0.95] and HR 0.73, 95%CI [0.57-0.92], respectively). Additional adjustment for propensity score for statin, beta-blocker and aspirin use did not influence these results (Figure 2).
The 5 years cumulative survival of all cause long-term mortality and MACCE were worse in patients with a hypertensive BP response without baseline statin (p-value 0.009 and 0.001), beta-blocker (p-value 0.001 and 0.001) or aspirin use (0.016 and 0.006) compared with patients with a normal BP response without these medications (Figure 3). In patients with hypertensive BP response cumulative survival of all cause long-term mortality and MACCE was better with baseline statin (p-value 0.068 and 0.017) beta-blocker (p-value 0.057 and 0.24) or aspirin use (p-value 0.45 and 0.42) compared with those who did not use these baseline medications (Figure 3).

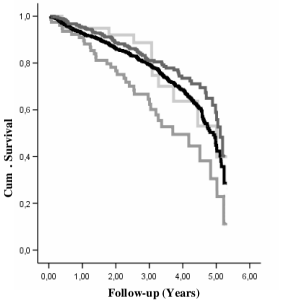
DISCUSSION

Our study showed that hypertensive BP response after a single-stage treadmill exercise tests in patients with known or suspected PAD was associated with all cause long-term mortality and MACCE. Importantly, this increased risk might be reduced by treatment of statins, beta-blockers and aspirin.
There are several mechanisms to explain the observed relationship between hypertensive BP response, mortality and cardiovascular events, as observed in our study. Patients with hypertensive BP response failed to show a decline in peripheral resistance in response to exercise compared with patients with a normal BP response [23]. This suggests failure in the capacity of exercise induced vasodilation, probably caused by poor arterial compliance resulting from generalised atherosclerosis, endothelial dysfunction or sympathetic nerve system dysfunction [24-27]. In addition, it is possible that due to generalised atherosclerosis, patients suffer from muscular ischemia during the exercise test, which results in an activation of the mechanosensitive or metabolsensitive reflex, a powerful pressure rising reflex in response to ischemia, resulting in an excessive rise in BP [24, 26].
Few studies previously investigated the relations among hypertensive BP response, cardiovascular diseases and mortality and if so, most were in healthy populations [2, 3, 6, 9]. Two studies investigated the effects of hypertensive BP response in patients with known or suspected coronary arterial disease [7, 28]. The first study investigated the association between hypertensive BP response and thallium perfusion defects [7, 28]. They found that a hypertensive BP response during an exercises test was associated with a lower likelihood of thallium perfusion defects compared with patients with a normal BP response, indicating a reduced severity of coronary artery disease. In addition, they observed no significantly increased risk of all cause mortality in patients with hypertensive BP response. However,

Figure 3. Survival curves of beta-blocker, statin and aspirin use in normal and hypertensive blood pressure response during exercise for long-term all cause mortality and major adverse cerebrovascular and cardiac events.





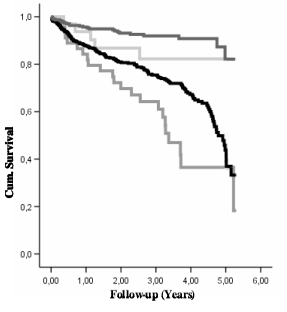


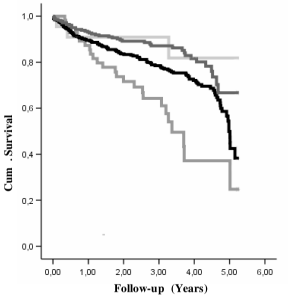
3a. All Cause Mortality

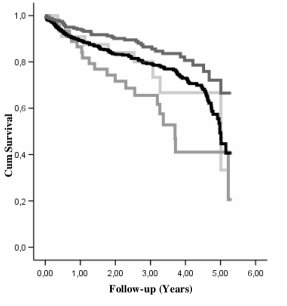
Normal blood pressure response no statin
Normal blood pressure response statin
Hypertensive blood pressure response no statin
Hypertensive blood pressure response statin

Normal blood pressure response no beta-blocker
Normal blood pressure response beta-blocker
Hypertensive blood pressure response no beta-blocker
Hypertensive blood pressure response beta-blocker

Normal blood pressure response no aspirin
Normal blood pressure response aspirin
Hypertensive blood pressure response no aspirin
Hypertensive blood pressure response aspirin







3b.MACCE

Normal blood pressure response no statin
Normal blood pressure response statin
Hypertensive blood pressure response no statin
Hypertensive blood pressure response statin

Normal blood pressure response no beta-blocker
Normal blood pressure response beta-blocker
Hypertensive blood pressure response no beta-blocker
Hypertensive blood pressure response beta-blocker

Normal blood pressure response no aspirin
Normal blood pressure response aspirin
Hypertensive blood pressure response no aspirin
Hypertensive blood pressure response aspirin

the investigators defined hypertensive BP response as a peak exercise systolic BP of ≥ 210 mmHg in men and ≥ 190 mmHg in women, according to the Framingham criteria, which were based on a healthy population without baseline hypertension [6]. Applying these Framingham criteria, more patients will meet the criteria for hypertensive BP response during exercise, due to the existence of baseline hypertension. This might explain the higher prevalence of patients with hypertensive BP response in that study compared with our study. To overcome this limitation, we defined hypertensive BP response in the current study as an increase in systolic BP at the exercise test of ≥ 55mmHg compared with the resting systolic BP. In addition, because Bassett et al. showed that the maximal exercise systolic BP strongly correlated with the resting systolic BP, we performed adjustments in the analysis including the resting systolic BP, which was not done by the study of Campbell et al [29]. The second study investigated the relation between hypertensive BP response and angiographic coronary arterial disease [7, 28]. The authors reported less severe coronary arterial disease and a lower mortality rate in patients with hypertensive BP response. However, they also used the Framingham criteria to define hypertensive BP response, which might have resulted in a misclassification, as mentioned above. In addition, they had a very short follow-up period of 2 years, with only 23 deaths in the total population.

We found that statin, beta-blocker and aspirin use in patients with hypertensive BP response were associated with a reduction in the risk of MACCE. No studies to date investigated the effects of these medications in patients with hypertensive BP response. A subgroup analysis in PAD patients of the Heart Protection Study collaborative group showed that simvastatin reduced major cardiac events [14]. The protective effect of statin use on mortality may be caused not only by the lipid-lowering effect, but also through an inhibitory effect of the inflammatory process observed in patients with atherosclerosis [17]. Beta-blockers have also been shown to have beneficial effects in patients with PAD [15, 18]. This is probably caused by prevention of plaque disruption accomplished by lowering heart rate, blood pressure and the anti-inflammatory properties [16, 20]. Aspirin, at present the drug of choice for prevention of cardiovascular events, irreversibly blocks platelet cyclooxygenase-1, which inhibits the production of tromboxane A2, resulting in a decreased platelet aggregation. Two large meta-analyses showed a reduction in major vascular mortality and MACCE in patients with PAD using aspirin [13, 19].

A limitation of our study was that medication use was not randomised. To overcome this problem, we performed additional adjustments using propensity scores, an effective statistical way to try to overcome the effects of possible selection bias [22].

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Prognostic value of hypotensive blood pressure response during single-stage exercise test on long-term outcome in patients with known or suspected peripheral arterial disease

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ABSTRACT

Objective: A decline in systolic blood pressure during exercise is thought to be a sign of severe coronary artery disease. However, no studies have yet examined this effect in patients with known or suspected peripheral arterial disease. Therefore, we investigated the prognostic value of hypotensive blood pressure response after single-stage exercise test on long-term mortality, major adverse cerebrovascular and cardiac events (MACCE) and the effects of statin, beta-blocker and aspirin use in patients with known or suspected peripheral arterial disease.

Methods: A total of 2022 patients were enrolled in an observational study with a mean follow-up of 5 years. Hypotensive blood pressure response, 4.6% of the total population, was defined as a drop in exercise systolic blood pressure below resting systolic blood pressure.

Results: Our study showed that hypotensive blood pressure response was associated with an increased risk of all cause mortality (HR 1.74, 95%CI [1.10-2.73]) and MACCE (HR 1.85, 95%CI [1.14-3.00]), independent of other clinical variables. Additionally, after adjustments for clinical risk factors and propensity score, baseline statin use was associated with a reduced risk of all cause mortality (HR 0.60, 95% CI [0.44-0.80]). Besides, statin and aspirin use were both also associated with a reduced risk of MACCE (HR 0.65, 95%CI [0.47-0.89] and HR 0.69, 95%CI [0.53-0.88], respectively).

Conclusion: Hypotensive blood pressure response after single-stage treadmill exercise tests in patients with known or suspected peripheral arterial disease was associated with a higher risk for all cause long-term mortality and MACCE, which might be reduced by statin and aspirin use.

INTRODUCTION

A normal blood pressure (BP) response during dynamic exercise is a rise in the systolic BP with no change or a slightly decrease in the diastolic BP and widening of the pulse pressure [1]. Some patients, however, show a decline in systolic BP during an exercise test. This hypotensive BP response is thought to be a sign of severe coronary artery disease (CAD). However the study results of the predictive value of this hypotensive BP response on cardiovascular diseases and death are conflicting. A few studies showed that, although a hypotensive BP response is infrequent, it was associated with severe coronary artery disease and cardiovascular death [2-5]. In contrast, some researches observed that hypotensive BP response is only associated with CAD in certain subgroups, whereas others found no association at all [6-9]. Most studies, however, have been performed in patients with known or suspected CAD. No studies have yet investigated the effects of hypotensive BP response during exercise test in patients with known or suspected peripheral arterial disease (PAD). In addition, the effects of statin, beta-blocker and aspirin use on mortality risk in patients with PAD has been investigated previously in a number of studies, but have not yet been discussed in patients with hypotensive BP response [10-17]. Therefore, to bridge these knowledge gaps, we performed an observational study to assess the predictive value of hypotensive BP after single-stage exercise test on long-term mortality, major adverse cerebrovascular and cardiac events (MACCE) and the effects of statin, beta-blocker and aspirin use in patients with known or suspected PAD.

METHODS

Study Population

Our study population consisted of 2022 patients, who were referred to the Erasmus Medical Centre, Rotterdam, the Netherlands, between July 1993 and December 2005, with a history of intermittent claudication, pain in the legs or other symptoms of arterial insufficiency such as ulcerations, for a single-stage treadmill walking test to diagnose or evaluate PAD. The hospitals medical ethical committee approved the study and patients gave permission to use their data.

Single-stage exercise test

Only specialised trained personnel executed the exercise tests, using a prescribed protocol. The systolic BP was measured with a blood pressure device (Maxi stable 3, presso stabl; Welch Allyn Inc, Skaneateles Falls, New York, USA) at both left and right arms in supine position after 15 minutes rest. In addition, the BP at the dorsalis pedis and posterial tibial arteries were measured at both sides, using a Doppler ultrasonic instrument with an

8-MHZ vascular probe (Imexdop CT+ vascular Doppler; Miami Medical, GlenAllen, Va). After these measurements all patients were asked to walk on a treadmill with a speed of 4 km/h for a maximum of 5 minutes. No inclining plane or graded inclines were used. During the walking test patients were ask to tell the personnel when they started to feel pain in the legs. Patients were encouraged to finish the whole test. The total walking time and distance were recorded. Immediately after the exercise the systolic BP at the arm, as well as at the dorsalis pedis or posterial tibial artery, depending which one was highest at rest, were measured in supine position. All variables were incorporated in a computerised hospital database.

Definition of Hypotensive BP response

Hypotensive BP response was defined as a drop of the exercise systolic BP below the resting systolic BP. Following these criteria, 93 patients (4.6%) developed a hypotensive BP response at the exercise test. Besides, we identified the 95th percentile of the increase systolic BP, the difference between the highest measure exercise systolic BP and the highest measured resting systolic BP, in those patients within our population without hypertension, chronic obstructive pulmonary disease, cardiovascular history or renal dysfunction. This 95th percentile turned out to be 55mmHg. Patients with an increase systolic BP of less than 55mmHg was defined as having a normal BP response. Patients who had an increase in systolic BP at the exercise test of 55mmHG or more were defined as having hypertensive BP response and were excluded from analyses, due to the different risk profile, as we have shown previously [18]. Ankle brachial index for both sides at rest and after the exercise test was calculated by dividing the the systolic BP at the dorsalis pedis or posterial tibial artery, depending which one was the highest, by the highest systolic BP at the arm.

Covariate assessment

From the medical records, the following baseline characteristics were collected: age, gender, current smoking, diabetes mellitus, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, renal dysfunction, angina pectoris, history of congestive heart failure, previous myocardial infarction, coronary artery revascularisation and baseline use of statin, beta-blocker or aspirin. The 12-lead electrocardiography was screened for abnormalities. Medical records were checked using patient history or echocardiography test results for severe valvular diseases. The following definitions were used for the different covariates. Diabetes mellitus was documented when patients presented with the diagnosis, made by the referred physician or required anti-diabetic medication. Hypertension was recorded if a patient had a blood pressure higher > 140/90mmHg or treated with antihypertensive medication. Chronic obstructive pulmonary disease was classified as a history of chronic obstructive pulmonary disease or pulmonary medication use. Hypercholesterolemia was noted when patients presented with the diagnosis, made by the

referred physician or received lipid-lowering medication. Renal dysfunction was defined as having a serum creatinine level of ≥2.0 mg/dl or receiving dialyses.

Follow-up

The follow-up of the vital status, which was obtained by reviewing the civil registries, was completed for 99.3%. The survival status of six patients who had moved abroad could not be retrieved, and the last available follow-up data were used. The cause of death was obtained from the civil registries or from medical records. Of 56 patients (10%) no course of death could be traced. Additionally, to all 1468 survivors, a self-reporting questionnaire about cardiac events were sent, whereof 73% returned the questionnaire.

Statistical methods

To identify differences in baseline characteristics and exercise results between hypotensive BP response and normal BP response student's t- tests for continuous variables were used and chi-square tests for categorical variables. Cox proportional hazard ratio's (HR) with 95% confidence interval (95% CI) were calculated to define the relationship between hypotensive BP response, long-term mortality, MACCE and statin, beta-blocker or aspirin use. MACCE consisted of cardiac or cerebrovascular death or major adverse cardiac events such as hospital admission for angina pectoris, non-fatal myocardial infarction diagnosed in a hospital defined as acute coronary syndrome with rise in troponin or rapid rise and fall of CK-MB, or pathologic findings of acute myocardial infarction, coronary artery bypass grafting or percutane transluminale coronair angioplasty. Adjustments were made for potential clinical risk factors (age, gender, current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases and renal failure, systolic BP at rest, lowest resting ankle brachial index). Additional adjustments were made with the propensity scores, a probability of being treated, calculated on the individual's covariates, to reduce the effects of selection bias [19]. For all test significance was defined as a p-value of ≤ 0.05. Analyses were performed in SPSS 14 for windows.

RESULTS

The mean age of the total population was 62 years and consisted of 67% of men. None of the 93 patients with hypotensive BP were known with a history of severe cardiac valvular disease. Besides, they were significant younger, had less often a history of coronary artery bypass grafting, showed less often electrocardiography abnormities at baseline and a lower percentage beta-blocker use (Table 1). The resting ankle brachial index as well as

Table 1. Baseline characteristics in patients with hypotensive and normal blood pressure response.

Characteristics	Hypotensive blood pressure response (n=93)	Normal blood pressure response (n=1929)	p-value
Male (%)	57 (61%)	1289 (67%)	0.3
Age (yrs)	**57 ± 15**	**62 ± 12**	**0.0001**
Body mass index (kg/m^2)	26 ± 4	26 ± 7	0.6
Chronic obstructive pulmonary disease	8 (9%)	248 (13%)	0.3
Hypertension	32 (35%)	694 (36%)	0.8
Diabetes	16 (17%)	321 (17%)	0.9
Current smoking	32 (35%)	617 (32%)	0.6
Hypercholesterolemia	23 (25%)	489 (26%)	0.9
Renal dysfunction	4 (4%)	127 (7%)	0.4
Angina Pectoris	11 (12%)	318 (17%)	0.2
History of cardiac disease	23 (25%)	653 (34.2%)	0.06
Previous myocardial infarction	15 (16%)	405 (21%)	0.2
Coronary artery bypass grafting	**4 (4%)**	**224 (12%)**	**0.03**
Percutaneous coronary intervention	4 (4%)	145 (8%)	0.2
Heart failure	8 (9%)	119 (6%)	0.3
Electrocardiography abnormalities	**15 (18%)**	**540 (31%)**	**0.01**
Medication use:			
Statin	25 (27%)	608 (32%)	0.4
Beta-blocker	**20 (22%)**	**608 (32%)**	**0.04**
Aspirin	24 (26%)	533 (28%)	0.7

Values are means with standard deviations or numbers with percentages.
Bold characters indicate significant p-value < 0.05.

the exercise ankle brachial index was significantly lower in patients with a hypotensive BP response compared to patients with a normal BP response (Table 2).

The mean follow-up period was 5 years, ranging from 0.5 to 14 years. During the follow-up period, 540 patients died, whereof 49% was of cardiac origin in the normal BP response group and 65% in the hypotensive BP response group. MACCE was recorded in 386 patients.

Patients with hypotensive BP response had an increased risk of long-term all cause mortality and MACCE compared to patients with normal BP response, independent of other clinical variables (Table 3).

Baseline statin use was associated with a significant reduced risk in all cause long-term mortality, independent of other clinical variables and independent of the propensity score (HR 0.60 95%CI [0.44-0.80]) (Figure 1). Beta-blocker and aspirin use were not significantly related with a reduced risk in all cause long-term mortality (HR 0.98 95%CI [0.79-1.20] and HR 0.90 95%CI [0.73-1.11], respectively) (Figure 1). However, statin as well as aspirin use were both significantly associated with a reduced risk of MACCE, independent

Table 2. Single-stage exercise test characteristics of hypotensive and normal blood pressure response.

Exercise test	Hypotensive blood pressure response (n=93)	Normal blood pressure response (n=1929)	p-value
Systolic blood pressure at rest (mmHg)	152 ± 31	150 ±26	0.5
Ankle brachial index at rest	**89 ± 25**	**77 ± 25**	**0.0001**
Ankle brachial index < 90 at rest (%)	**39 (43)**	**1167 (61)**	**0.0001**
Total walking distance (meters)	225 ± 115	227 ± 99	0.9
Systolic blood pressure after exercise (mmHg)	**138 ± 33**	**173 ± 31**	**0.0001**
Ankle brachial index after exercise	**88 ± 39**	**60 ± 32**	**0.0001**
Ankle brachial index < 90 after exercise (%)	**39 (43)**	**1406 (73)**	**0.0001**

Values are means with standard deviations or numbers with percentages.

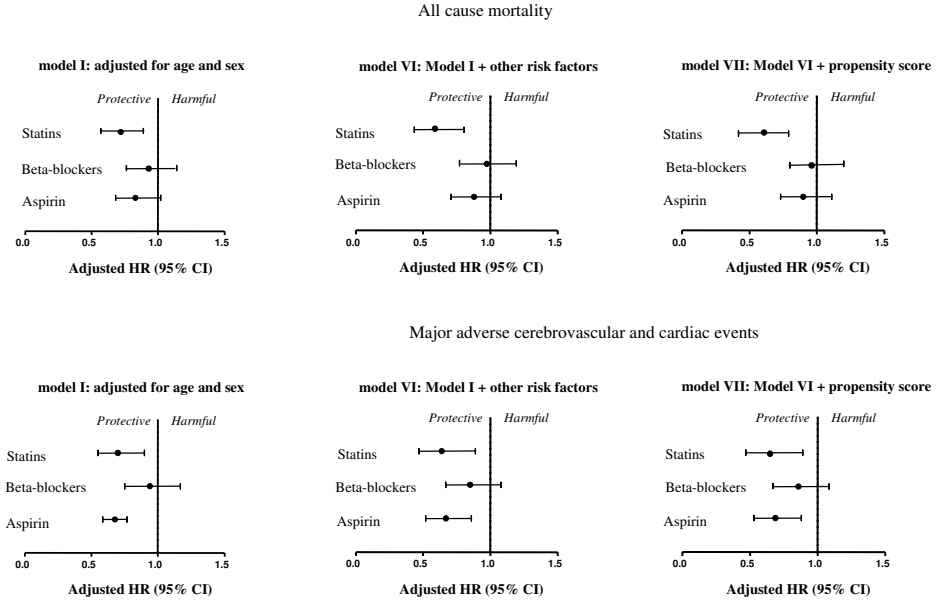
of other clinical variables (HR 0.64 95%CI [0.47-0.89] and HR 0.69 95%CI [0.53-0.88], respectively) (Figure 1). Additional adjustment for the propensity score did not influence these results. Although beta-blocker use also showed a reduced risk of MACCE, it did not reach significance (HR 0.85 95%CI [0.67-1.08]) (Figure 1).

Table 3. Adjusted hazard ratios (HR) with 95% confidence interval (CI) of long-term all cause mortality and major adverse cerebrovascular and cardiac events in patients with a hypotensive compared with a normal blood pressure response (BPR).

Model	I (HR, 95%CI)	II (HR, 95%CI)	III (HR, 95%CI)	IV (HR, 95%CI)
Normal BPR	1.0	1.0	1.0	1.0
Hypertensive BPR				
All cause mortality	**1.62 (1.04-2.51)**	**1.73 (1.11-2.69)**	**1.69 (1.09-2.64)**	**1.74 (1.10-2.73)**
Major adverse cerebrovascular and cardiac events	**1.59 (1.00-2.53)**	**1.84 (1.15-2.94)**	**1.76 (1.10-2.81)**	**1.85 (1.14-3.00)**

Model I = age and gender
Model II = Model I + current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases and renal failure
Model III = Model II + systolic blood pressure at rest
Model IV = Model II + systolic blood pressure at rest + ankle brachial index at rest
Bold characters indicate significant p-value < 0.05

Figure 1. The effect of statin, beta-blocker and aspirin use in patients with hypotensive blood pressure response on long-term all cause mortality and major adverse cerebrovascular and cardiac events.



DISCUSSION

This study showed that hypotensive BP response after a treadmill single-stage exercise tests in patients with known or suspected PAD was associated with a higher risk for all cause long-term mortality and MACCE, which might be reduced by statin and aspirin use. During dynamic exercise, a rise in systolic BP with no changes or slightly decrease in diastolic BP, resulting in widening of the pulse pressure, is considered as a normal BP response [1]. Some patients, however, show a decline in systolic BP during an exercise test, which is thought to be an abnormal exercise response. A few mechanisms are associated with this hypotensive BP response at exercise. Sometimes it occur in normal subjects, mostly after prolonged and vigorous exercise [1, 20]. Hypovolemia and valvular disease can also produce a hypotensive BP response at exercise, as well as medication use, such as beta-blockers [1, 21]. However, the most commonly used explanation for the hypotensive BP response at exercise, is heart failure or left ventricular dysfunction resulting from CAD [1-3, 22]. Nevertheless, study results of the predictive value of this hypotensive BP response on cardiovascular diseases and death are conflicting. Some studies showed that a hypotensive BP response was associated with severe CAD (three vessel or left mean coronary disease), extent perfusion abnormalities on thallium scintigraphy and exercise induced left ventricular dysfunction [2, 3, 22]. Both Morris et al. and Prakash et al. found that

hypotesive BP response at exercise was associated with an increased risk of cardiovascular and all cause mortality [4, 5]. In contrast, others found no association between hypotensive BP response and cardiovascular morbidity or mortality, although their number of patients with hypotensive BP response, number of events or follow-up time were limited [8, 9]. Furthermore, other studies observed that hypotensive BP response was only associated with CAD in certain subgroups [6, 7]. Nevertheless, most studies have been performed in patients with known or suspected CAD. No studies have yet investigated the relationship between hypotensive BP response during exercise test and long-term all cause mortality and MACCE in patients with known or suspected PAD.

In this study statin and aspirin use in patients with hypotensive BP response was associated with a reduction in the risk of all cause mortality or MACCE. Beta-blocker use showed a reduced risk of MACCE, although it did not reach significance. No studies have yet investigated the effects of these medications in patients with hypotensive BP response. A subgroup analysis in PAD patients of the Heart Protection Study Collaborative Group showed that simvastatin reduced major cardiac events [11]. The protective effect of statin use on mortality may not only be due to the lipid-lowering effect, but also through an inhibitory effect of the inflammatory process observed in atherosclerosis [14]. Aspirin, at present the drug of choice for prevention of cardiovascular events, irreversibly blocks platelet cyclooxygenase-1, which inhibits the production of tromboxane A2, resulting in a decreased platelet aggregation. Two large meta-analyses both showed a reduction of major vascular mortality and cerebro- and cardiovascular events in patients with PAD using aspirin [10, 16]. Beta-blockers have also been shown to have beneficial effects in patients with PAD [12, 15]. This is probably due to prevention of plaque disruption accomplished by lowering heart rate, blood pressure and anti-inflammatory properties [13, 17].

Besides the limitations of the missing values of MACCE and cardiac deaths and limited number of BP measurements (only before and after the exercise test), the major limitation of this study is that the medication use was not randomised. However, to overcome this limitation, we performed additional adjustments with propensity scores, an effective statistical way to try to overcome the effects of possible selection bias [19].

In conclusion, a hypotensive BP response after a single-stage treadmill exercise tests in patients with known or suspected PAD was associated with a higher risk for all cause long-term mortality and MACCE, which might be reduced by statin and aspirin use.

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Exercise blood pressure response is associated with perioperative complications at major vascular surgery

5

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Submitted; Coron Artery Dis

ABSTRACT

Background: Previous studies have shown that hypertensive or hypotensive blood pressure response during a pre-operative treadmill exercise test in patients with peripheral arterial disease (PAD) is associated with a two fold increased risk of cardiovascular events and mortality. However, it is unknown if these patients also experience an increased perioperative complication risk at major vascular surgery.

Methods: In total 665 consecutive PAD patients underwent elective major vascular surgery (carotid endarterectomy, abdominal aorta repair or lower extremity revascularization). perioperative complications (infection, myocardial infarction, angina pectoris, cardiac arrhythmia, heart failure, cerebrovascular accident or spinal cord ischemia, dialyses, amputation, thrombectomy, re-operation or death) defined as occurring within 30 days after surgery were collected using medical records. Hypertensive blood pressure response was defined as a difference between exercise systolic blood pressure and resting systolic blood pressure of more than 55mmHg. Hypotensive blood pressure response was defined as a drop in exercise systolic blood pressure below resting systolic blood pressure.

Results: Patients with a hypertensive blood pressure response during a pre-operative exercise test (n=66) demonstrated a higher risk of early perioperative thrombectomy (HR 2.80 95%CI (1.24 - 6.33)) compared to patients with a normal blood pressure response (n=582). Patients with a hypotensive blood pressure response (n=18) showed an increased risk of perioperative myocardial infarction (HR 3.69 95% CI (1.08 - 12.64)) and cardiac complications (HR 2.90 95% CI (1.02-8.19)) compared to patients with a normal blood pressure response.

Conclusion: Patients with an abnormal blood pressure response have more cardiovascular complications at elective major vascular surgery.

INTRODUCTION

During dynamic exercise, systolic blood pressure normally rise with no change or a slightly decrease in the diastolic blood pressure and widening of the pulse pressure [1]. However, some patients show a decline in systolic blood pressure during an exercise test. This hypotensive blood pressure response is thought to be a sign of heart failure or left ventricular dysfunction due to severe coronary artery disease [1-4]. Other patients may demonstrate a hypertensive blood pressure response which is thought to be due to failure of the exercise induced vasodilation, resulting from generalised atherosclerosis [5-8]. We previously showed that both a hypertensive and hypotensive blood pressure response during a treadmill exercise test in patients with known or suspected peripheral arterial disease (PAD) were associated with increased risk of cardiovascular events and mortality [9, 10]. However, it is unknown whether these patients also experience more complication risks at major elective vascular surgery.

Therefore, we performed a retrospective study to investigate whether patients with a hypertensive or hypotensive blood pressure response have a higher complication risk at major elective vascular surgery.

METHODS

Study Population

Our baseline study population consisted of 2191 consecutive patients, who were referred by general practitioners or physicians to the vascular laboratory of the Erasmus Medical Centre, Rotterdam, the Netherlands, for a single-stage treadmill exercise test, between 1993 and 2006. Patients were referred by physicians to diagnose PAD, based on their presenting symptoms, or to evaluate their PAD. Excluded were patients who were unable to perform the treadmill exercise test and those who underwent rescue vascular surgery

Single-stage treadmill exercise test

Specialised trained personnel supervised the exercise tests, using a prescribed protocol. Details on the protocol have been previously reported [9-12]. Briefly, the systolic blood pressure was measured in supine position after 15 minutes rest. In addition, the blood pressure at the dorsalis pedis and posterial tibial arteries were measured at both sides. Then, all patients were asked to walk on a treadmill with a speed of 4 km/h for a maximum of 5 minutes. No inclining plane or graded inclines were used. Immediately after the exercise the systolic blood pressure at the arm, as well as at the dorsalis pedis or posterial tibial artery, depending which one was highest at rest, were measured again in supine position. ABI at rest and after the exercise test were calculated by dividing the systolic blood pres-

sure at the dorsalis pedis or posterial tibial arteries, depending which one was the highest, by the highest systolic blood pressure at the arm.

Definitions of normal, hypertensive and hypotenive blood pressure response

Hypotensive blood pressure response was defined as a drop in exercise systolic blood pressure below resting systolic blood pressure [10]. For the definition of a hypertensive blood pressure response, as we described previously, we identified the 95th percentile of the difference between the exercise systolic blood pressure and resting systolic blood pressure, which was 55mmHg [9]. Patients with an increase in systolic blood pressure of more than 55mmHg were defined as having a hypertensive blood pressure response. Patients who had an increase in systolic blood pressure of less than 55mmHG were defined as having a normal blood pressure response. Details and discussion about the definitions of hypotensive and hypertensive blood pressure response have been previously reported [9-10].

Covariate assessment

From the medical records, the following baseline characteristics were collected: age, gender, current smoking, diabetes mellitus, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, 12-lead electrocardiography abnormality's, renal dysfunction, history of congestive heart failure, history of cardiac disease consisted of angina pectoris, myocardial infarction or coronary artery revascularisation. The following definitions were used for the different covariates. Diabetes mellitus was documented when patients presented with the diagnosis, made by the referred physician, required anti-diabetic medication, having a fasting glucose level ≥ 126mg/dl, a glucose level of ≥ 200mg/dl after a oral glucose tolerance test or plasma non-fasting glucose levels of ≥ 200mg/dl [13, 14]. Hypertension was recorded if a patient had a blood pressure higher > 140/90mmHg or treated with antihypertensive medication. Chronic obstructive pulmonary disease was classified as a history of chronic obstructive pulmonary disease or pulmonary medication use. Hypercholesterolemia was noted when patients presented with the diagnosis, made by the referred physician, received lipid-lowering medication or a plasma cholesterol level of 212mg/dl or more. The 12-lead electrocardiography was screened for abnormalities, such as left ventricular hypertrophy, q-waves, left bundle brache block, st-depression or elevation. Renal dysfunction was defined as having a serum creatinine level of ≥2.0 mg/dl or receiving dialyses.

Perioperative complications at major vascular surgery

From our baseline study population, consisted of 2191 patients, 665 patients underwent elective major vascular surgery (carotid endarterectomy, abdominal aorta repair or lower extremity revascularization surgery. Endovascular repair were excluded) in the Erasmus MC after their treadmill exercise test. Perioperative complications and data of occurrence were defined as occurring within one month after the major vascular surgery and were

collected using the complication registrations, medical records and computerised hospital databases. Vital status and cause of death was obtained by reviewing the Central Bureau of Statistics and medical records. Infection was defined as wound infection, urinary infection or pneumonia when needed treatment (surgical intervention or antibiotic therapy). Perioperative myocardial infarction within one month after the surgery was defined using the criteria of ESC and ACC/AHA guidelines: increase and gradual decrease in troponin or more rapid increase and decrease in CK-MB with one of the following: ischemic symptoms, pathologic Q-wave on the electrocardiogram, new ST-segment elevations, ST-depression or T-wave abnormalities only (15, 16). Angina pectoris was recorded when a patient expressed chest pain, which was not from pain of the surgical wound and did not fulfil the criteria for perioperative myocardial infarction. Cardiac arrhythmia was defined as a new arrhythmia, not present on the preoperative 12-lead electrocardiogram. Heart failure was defined when it was mentioned in the medical record and needed treatment. Loss of neurological function by spinal cord ischemia or a cerebrovascular accident confirmed by CT scans within one month of the surgery was defined as neurological complication. Dialyses was recorded when a patient needed renal replacement therapy (CVVH or dialyses) within a month after the surgery and who did not received renal replacement therapy before surgery. Large haematoma or haemorrhage with needed treatment were defined as haemorrhage. The requirement of an amputation or thrombectomy within one month of the major vascular surgery was classified as amputation and thrombectomy. The need for a re-operation within one month related to the previous surgery was defined as re-operation. Total perioperative complications were all complications combined which occurred within one month of surgery. Perioperative myocardial infarction, angina pectoris, heart failure and new cardiac arrhythmia's together were classified as cardiac complications.

Statistical methods

To identify differences in baseline characteristics between patients with a normal blood pressure response, hypertensive and hypotensive blood pressure response student's t- tests for continuous variables were used and chi-square tests for categorical variables. Cox proportional hazard ratio's (HR) with 95% confidence interval (95% CI) were calculated to define the relationship between hypertensive and hypotensive blood pressure response and perioperative complications. By using a multivariate analyses adjustments were made for potential clinical risk factors, such as age, gender, current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, electrocardiography abnormalities, renal failure, systolic blood pressure at rest, exercise ankle brachial index and time between the exercise test and surgery. For all tests significance was defined as a P-value of ≤ 0.05. Analyses were performed in SPSS 15 for windows.

RESULTS

Mean age of the total population (n=665) was 64 years with 75% males. No differences were observed in baseline characteristics between patients with normal, hypertensive and hypotensive blood pressure response, except for the exercise brachial index, with the lowest value in patients with a hypertensive blood pressure response (Table 1). Overall, 32 patients (5%) underwent carotid endarterectomy, 165 (25%) abdominal aorta repair and 468 (70%) lower extremity revascularization. The percentage of perioperative complications for the total population ranged from 1% for angina pectoris till 15% for infections

Table 1 Baseline characteristics of patients with normal, hypertensive and hypotensive blood pressure response.

Characteristics	Normal blood pressure response N=582	Hypertensive blood pressure response N=66	Hypotensive blood pressure response N=17	P-value
Age (years)	63 ± 11	65 ± 9	62 ± 10	NS
Body mass index (kg/m^2)	26 ± 9	26 ± 5	26 ± 8	NS
Male (%)	441 (76)	51 (77)	14 (83)	NS
Chronic obstructive pulmonary disease (%)	98 (17)	12 (18)	3 (19)	NS
Hypertension (%)	227 (39)	24 (36)	9 (53)	NS
Diabetes mellitus (%)	92 (16)	13 (20)	4 (23)	NS
Current smoking (%)	170 (29)	14 (21)	5 (29)	NS
Hypercholesterolemia (%)	154 (27)	13 (20)	2 (12)	NS
Renal failure (%)	29 (5)	2 (3)	1 (6)	NS
Abnormal ECG	386 (67)	36 (55)	13 (77)	NS
History of heart failure (%)	37 (6)	3 (5)	2 (12)	NS
History of cardiac disease (%)	221 (38)	24 (36)	7 (41)	NS
Aspirin (%)	167 (29)	16 (24)	5 (29)	NS
Beta-blocker use (%)	181 (31)	23 (35)	7 (41)	NS
Statin use (%)	187 (32)	20 (30)	3 (18)	NS
Resting systolic blood (mmHg)	156 ± 28	156 ± 21	156 ± 28	NS
Resting ankle brachial index	64 ± 22	63 ± 24	67 ± 28	NS
Exercise ankle brachial index	**43 ± 28**	**35 ± 25**	**53 ± 39**	**0.028**
Type of surgery (%)				NS
Carotid endarterectomy	27 (5)	4 (6)	1 (6)	
AAA or abdominal aorta repair	153 (26)	11 (17)	1 (6)	
Lower extremity revascularization	402 (69)	51 (77)	15 (88)	

Values are means with standard deviations or numbers with percentages.
Bold numbers are significant different with P-value<0.05

and re-operations. The 30 day mortality was 3%. The complication rates for the three different groups are shown in Table 2.

Patients with a hypertensive blood pressure response demonstrated a higher risk of thrombectomy after the major vascular surgery (HR 2.80, 95%CI (1.24 - 6.33)) compared to patients with a normal blood pressure response (Table 3). No associations with other perioperative complications were observed.

This was in contrast to patient with a hypotensive blood pressure response. These patients showed after adjustments for potential clinical risk factors an increased risk for perioperative myocardial infarction (HR 3.69, 95% CI (1.08 - 12.64)) compared to patients with a normal blood pressure response (table 3). Similar results were seen for cardiac complications (HR 2.98, 95% CI (1.05-8.47) and when perioperative cardiac complications were combined with 30-day cardiac mortality (HR 2.90, 95% CI (1.02-8.19) (table 3).

Table 2 Complication rates of patients with normal, hypertensive and hypotensive blood pressure response.

Complications	Normal blood pressure response N=597	Hypertensive blood pressure response N=68	Hypotensive blood pressure response N=18
Infection (%)	88 (15)	10 (15)	1 (6)
Myocardial infarction (%)	39 (7)	4 (6)	3 (18)
Angina pectoris (%)	8 (2)	1 (2)	0
Heart failure (%)	14 (3)	2 (3)	1 (6)
Cardiac arrhythmia's (%)	22 (4)	2 (3)	1 (6)
Neurological (%)	11 (2)	1 (2)	0
Dialyses (%)	12 (2)	1 (2)	0
Hemorrhage (%)	24 (4)	3 (5)	0
Amputation (%)	16 (3)	1 (2)	0
Thrombectomy (%)	27 (5)	8 (12)	1 (6)
Re-operation (%)	83 (14)	9 (14)	1 (6)
30-day mortality (%)	21 (4)	1 (2)	0
Total complications (%)	193 (33)	23 (35)	4 (24)
Cardiac complications (%)	62 (11)	7 (11)	4 (24)
Cardiac complications with 30-day mortality (%)	65 (11)	7 (11)	4 (24)

Values are numbers with percentages.

Table 3 Hazard ratios (HR) with 95% confidence interval (CI) of complications after surgery in patient with hypertensive and hypotensive blood pressure response.

Complications	Normal blood pressure response (reference)	Hypertensive blood pressure response (HR ,95% CI)		Hypotensive blood pressure response (HR ,95% CI)	
Infection (%)	1	1.02	(0.53 - 1.96)*	0.38	(0.05 - 2.70)*
		0.93	(0.48 - 1.88)¶	0.39	(0.05 - 2.80)¶
Myocardial infarction (%)	1	0.83	(0.30 - 2.33)*	2.96	(0.91 - 9.57)*
		1.04	(0.36 - 3.00)¶	**3.69**	**(1.08 - 12.64)**¶
Thrombectomy (%)	1	**2.70**	**(1.26 - 6.17)***	1.22	(0.17 - 8.99)*
		2.80	**(1.24 - 6.33)**¶	1.81	(0.24 - 13.78)¶
Re-operation (%)	1	1.00	(0.50 - 2.01)*	0.40	(0.06 - 2.89)*
		1.04	(0.52 - 2.11)¶	0.42	(0.06 - 3.06)¶
Total complications (%)	1	1.04	(0.68 - 1.61)*	0.74	(0.28 - 2.00)*
		1.11	(0.71 - 1.73)¶	0.92	(0.34 - 2.49)¶
Cardiac complications (%)	1	0.93	(0.42 - 2.03)*	2.51	(0.91 - 6.90)*
		1.11	(0.50 - 2.45)¶	**2.98**	**(1.05 - 8.47)**¶
Cardiac complications with 30-day mortality (%)	1	0.88	(0.40 - 1.92)*	2.39	(0.87 - 6.57)*
		1.07	(0.49 - 2.38)¶	**2.90**	**(1.02 - 8.19)**¶

* adjusted for age and gender

¶ adjusted for age, gender, current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, renal failure, resting systolic blood pressure, exercise ankle brachial index and time between exercise test and surgery

Bold numbers are significant different with P-value <0.05

DISCUSSION

In this study, it was shown that a pre-operative hypertensive blood pressure response was associated with an increased risk of thrombectomy shortly after major elective vascular surgery and patients with a pre-operative hypotensive blood pressure response had more myocardial infarction and cardiac complications.

We previously observed that patients with known or suspected PAD, who showed a hypertensive or hypotensive blood pressure response at a treadmill exercise test to diagnose or evaluate their PAD, were of a two fold increased risk of cardiovascular events and mortality compared to patients with a normal blood pressure response [9, 10]. But to the best of our knowledge no other studies have been performed to investigate the relationship between an abnormal blood pressure response and complication risk at major vascular surgery. Therefore, the mechanism why a hypertensive blood pressure response is related with an increased risk of surgery related thrombectomy is unknown. However, it can be hypothesised that dysfunction of the vascular endothelium might play an important role. As already explained before, during exercise the proportion of the cardiac output received by the skeletal muscles increases from 20% to 80%, due to exercise induced vasodilata-

tion [5, 8-10]. It is observed that patients with a hypertensive blood pressure response failed to show a decline in peripheral resistance [17]. This suggests a failure in the capacity of exercise induced vasodilation, which might be a result of endothelial dysfunction [6, 18]. Vascular endothelium is an imported regulator of vascular tone by producing vasodilattating compounds such as NO [8, 19]. Besides the vasodilatating effect, NO also plays a role in the inhibition of inflammation, platelet adhesion and tissue-factor release [20, 21]. In endothelial dysfunction there is a decrease in NO and an increase in vasocontrictors such as angiotensin II, resulting in vasoconstriction, vascular inflammation, platelet activation, trombosis and atherosclerosis [20, 21]. Other studies have shown that patients with PAD have endothelial dysfunction [20, 21]. Due to this endothelial dysfunction they are in a prothrombotic state [22-24]. Furthermore, a previous study observed that endothelial dysfunction was also associated with an abnormal systolic blood pressure response [8]. All together it can be hypothesised that patients with a hypertensive blood pressure response may suffer of a severe endothelial dysfunction, resulting not only in a more profound vasoconstriction but also in a protrombotic state which may cause an increased risk of re-trombosis [25]. However, future research is needed to confirm this hypothesis.

In patients with a hypotensive blood pressure response, more perioperative myocardial infarction and cardiac complications were observed. We previously showed that patients suspected for PAD with a hypotensive blood pressure response at a treadmill exercise test, had higher mortality rate and adverse cardiac events [10].The explanation for the increased risk of cardiac morbidity and mortality in patients with a hypotensive BP response at exercise is that the hypotensive BP response is due to heart failure or left ventricular dysfunction resulting from severe coronary artery disease [1-4]. This may also explain why patients with a hypotensive blood pressure response suffer of more perioperative cardiac events. As far was we are known of only one study observed that hypotension during a dobutamine echocardiography was associated with peri-operative cardiovascular events [26].

Our study has its limitations. The most important limitation is the retrospective design of the study. Complications were obtained by complication registrations, medical files and computerised hospital databases. Although, the complication rate, was comparable with the complication rates mentioned by other studies there will be an underestimation of reported complications and the actually complications [23, 27-32]. However, we don't expect selection bias with respect to abnormal blood pressure response and perioperative complications, as the possible complications which were missed are likely to be equivalent divided between the three patient groups.

In conclusion, patients with an abnormal blood pressure response at their pre-operative exercise treadmill test, have more cardiovascular complications after elective major vascular surgery. Additional prospective research is needed to confirm these results and to investigate the underlying mechanisms and which therapy is effective to prevent these complications.

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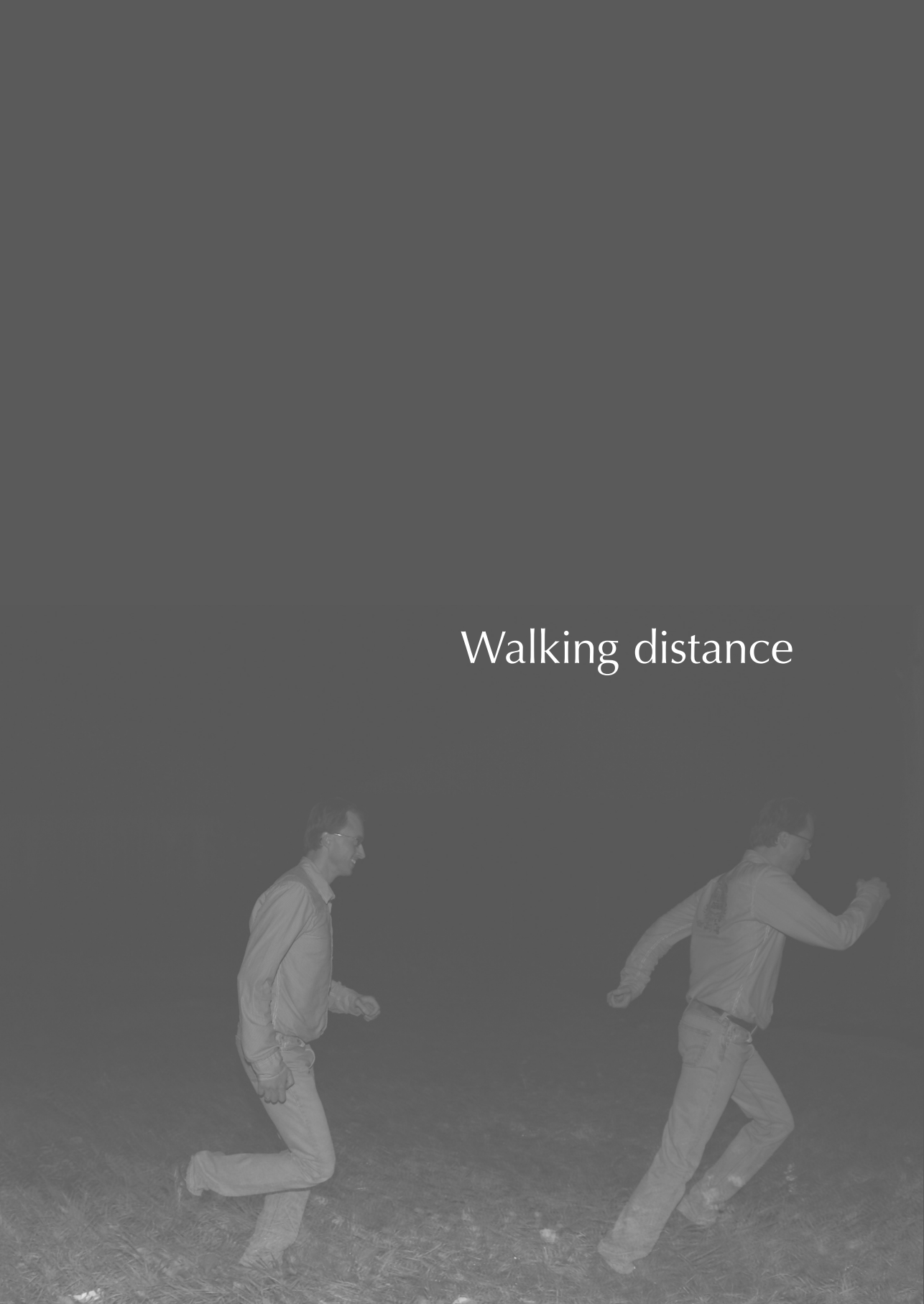
Walking distance



The prognostic value of impaired walking distance on long-term outcome in patients with known or suspected peripheral artery disease

6

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ABSTRACT

Objectives: To assess predictive value of walking distance after an exercise test on long-term out-come in patients with normal and impaired ankle brachial index (ABI).

Design: A total of 2191 patients with known or suspected peripheral artery disease (PAD), who were referred for a single-stage treadmill exercise test to diagnose or evaluate their PAD, were enrolled in an observational study between 1993 and 2006.

Materials and methods: Patients were divided into two groups: normal ABI (≥ 0.90) and impaired ABI (<0.90). Walking distance was divided into quartiles (no (reference), mild, moderate or severe impairment).

Results: In patients with normal ABI, severe walking distance was, after adjustment, associated with higher mortality risk (HR 2.60, (1.16-5.78)).

In patients with impaired ABI, all walking distance impairment quartiles, were associated with higher mortality (mild: HR 1.26 (0.95-1.67), moderate: HR 1.52 (1.13-2.05) and severe: HR 1.69 (1.26-2.27)). Furthermore, comparable associations were observed between all walking distance quartiles, cardiac death or major adverse cerebrovascular and cardiac events.

Conclusions: Our study illustrated that walking impairment is a strong prognostic indicator of long-term outcome in patients with impaired and normal ABI, which should be a warning sign to physicians to monitor these patients carefully and to provide them optimal treatment.

INTRODUCTION

Peripheral arterial disease (PAD) is associated with an increased risk of cardiovascular morbidity and mortality [1, 2]. To diagnose or to evaluate PAD, the ankle brachial index (ABI), the ratio between the ankle and brachial systolic blood pressure, is used [2, 3]. Several studies have shown that ABI is an independent risk factor for cardiovascular diseases and mortality [1, 2, 4-7]. Patients with PAD experience significant limitation in their physical functioning and walking in particular [8-13]. However, in contrast to the clinical value of the ABI, the clinical value of this walking disability is still unclear. It has been shown previously that in patients with impaired left ventricular function or congestive heart failure, the distance during a 6-minute walk test was a strong and independent predictor of morbidity and mortality [14]. In addition, a large cohort study in well-functioning community-based older adults observed that the inability to complete a 400meter walking test resulted in a higher mortality rate and more cardiovascular events and mobility limitations [15]. Nevertheless, only very few studies investigated the effects of physical activity on long-term outcome and is mostly performed in patients with impaired ABI [16-19]. Therefore, we performed a large observational study to assess the predictive value of the walking distance after a single-stage exercise test on long-term all cause mortality, cardiac death and major adverse cerebrovascular and cardiac events (MACCE) in patients with normal and impaired ABI.

MATERIALS AND METHODS

Study Population

Our study population consisted of 2191 patients, who were referred by general practitioners or physicians to the vascular laboratory of the Erasmus Medical Centre, Rotterdam, the Netherlands, for a single-stage treadmill exercise test, between 1993 and 2006. Our population represents a mixture of daily clinical practice of our vascular laboratory. Patients were referred by physicians to diagnose PAD, based on their presenting symptoms. Or patients, who already had a history of intermittent claudication or other symptoms of arterial insufficiency, were sent to evaluate their PAD. Excluded were patients who were unable to perform the treadmill exercise test. The hospital medical ethic committee approved the study and patients gave permission to use their data.

Single-stage exercise test

Specialised trained personnel supervised the exercise tests, using a prescribed protocol. The systolic blood pressure was measured with a blood pressure device (Maxi stable 3, presso stabl; Welch Allyn Inc, Skaneateles Falls, New York, USA) at both left and right arms in supine position after 15 minutes rest. In addition, the blood pressure at the dorsalis pedis and

posterial tibial arteries were measured at both sides, using a Doppler ultrasonic instrument with a 8-MHZ vascular probe (Imexdop CT+ vascular Doppler; Miami Medical, GlenAllen, Va). After these measurements all patients were asked to walk on a treadmill with a speed of 4 km/h for a maximum of 5 minutes. No inclining plane or graded inclines were used. During the walking test patients were ask to tell the personnel when they started to feel pain in the legs. Patients were encouraged to finish the whole test, but stopped when the patient was unable to walk further. Time and walking distance till the occurrence of leg pain and the total walking time and distance were recorded. Immediately after the exercise the systolic blood pressure at the arm, as well as at the dorsalis pedis or posterial tibial artery, depending which one was highest at rest, were measured in supine position. ABI at rest and after the exercise test were calculated by dividing the systolic blood pressure at the dorsalis pedis or posterial tibial arteries, depending which one was the highest, by the highest systolic blood pressure at the arm. As described previously, the interobserver and intraobserver agreement for the resting ABI was 97% and 98%, and for the exercise ABI 96% and 97% [4]. All variables were incorporated in a computerised hospital database. Patients were defined as having an impaired ABI, when the lowest resting or exercise ABI was < 0.90. Following these criteria, 1624 patients (74%) were considered as having an impaired ABI.

Covariate assessment

From the medical records, the following baseline characteristics were collected: age, gender, current smoking, diabetes mellitus, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, baseline medication use (statin, beta-blockers, ace-inhibitors and aspirin), renal dysfunction, history of congestive heart failure, history of cardiac disease consisted of angina pectoris, myocardial infarction or coronary artery revascularisation. The following definitions were used for the different covariates. Diabetes mellitus was documented when patients presented with the diagnosis, made by the referred physician, required anti-diabetic medication, having a fasting glucose level ≥ 126mg/dl, a glucose level of ≥ 200mg/dl after a oral glucose tolerance test or plasma non-fasting glucose levels of ≥ 200mg/dl [20, 21]. Hypertension was recorded if a patient had a blood pressure higher > 140/90mmHg or treated with antihypertensive medication. Chronic obstructive pulmonary disease was classified as a history of chronic obstructive pulmonary disease or pulmonary medication use. Hypercholesterolemia was noted when patients presented with the diagnosis, made by the referred physician, received lipid-lowering medication or a plasma cholesterol level of 212mg/dl or more. Renal dysfunction was defined as having a serum creatinine level of ≥2.0 mg/dl or receiving dialyses.

Follow-up

The follow-up vital status, which was obtained by reviewing the civil registries, was completed for 99.4%. The survival status of six patients who had moved abroad could

not be retrieved, and the last available follow-up data were used. The cause of death was obtained from the Central Bureau of Statistics or from medical records. Of 56 patients (10%) no course of death could be traced. Additionally, to all survivors, a self-reporting questionnaire about cardiac events were sent, of whom 73% returned the questionnaire.

Statistical methods

The exercise total walking distance were categorised into quartiles (no (reference), mild, moderate, severe walking impairment) for each group. Cox proportional hazard ratio's with 95% confidence interval (95% CI) were calculated to define the relationship between the exercise total walking distance and long-term all cause mortality, cardiac death and MACCE. MACCE consisted of cardiac or cerebrovascular death or major adverse cardiac events such as angina pectoris, non-fatal myocardial infarction, coronary artery bypass grafting or percutaneous coronary angioplasty. Adjustments were made for potential clinical risk factors and exercise ABI. All analyses were repeated after excluding patients with diabetes mellitus. The Kaplan Meier method with log-rank tests was used to compare survival of the four quartiles of the total walking distance. For all test significance was defined as a p-value of ≤ 0.05. Analyses were performed in SPSS 14 for windows.

RESULTS

Mean age of the total population was 62 years and 67% were men. Table 1 showed baseline characteristics of patients with impaired and normal ABI. Patients with impaired resting ABI were older, more males, had more often hypertension and were more often current smokers. As expected, the total walking distance was less in patients with impaired ABI compared to patients with normal resting ABI. In patients with normal ABI the total walking distance for the four quartiles were: 321 meters or more in the no impairment (reference) group, between 312-321 meters in mild impairment group, between 174-312 meters in moderate impairment group and 174 meters or less in the severe impairment group. In the patients with impaired ABI, the total walking distance in the patients with no impairment (reference) was 318 meters or more, mild impairment was between 233 and 318 meters, moderate impairment between 126-233 meters and patients with a severe impairment had a walking distance of 126 meter or less.

The mean follow-up period was 5 years, ranging from 0.5 to 14 years. During the follow-up period, 13% patients with normal ABI died and 34% in the impaired ABI group. Cardiac death and MACCE occurred in 5% and 12% in patients with normal ABI and 19% and 36% in the impaired ABI group.

In patients with normal ABI, a severe impairment in exercise total walking distance was, after adjustments of clinical risk factors and exercise ABI, independently associated with

Table 1. Baseline characteristics in patients with normal and impaired ankle brachial index.

Characteristics	Patients with normal ankle brachial index (n=562; 26%)	Patients with impaired ankle brachial index (n=1624; 74%)
Age (years)	59 ± 14	64 ± 11
Body mass index (kg/m^2)	26 ± 5	26 ± 7
Male (%)	338 (60)	1131 (70)
Chronic obstructive pulmonary disease (%)	62 (11)	220 (14)
Hypertension (%)	161 (29)	639 (40)
Diabetes mellitus (%)	91 (16)	322 (20)
Smoking (%)	147 (26)	555 (35)
Hypercholesterolemia (%)	121 (22)	435 (27)
Renal failure (%)	37 (7)	103 (6)
History of cardiac disease (%)	160 (29)	567 (35)
History of heart failure (%)	31 (6)	101 (6)
Exercise test:		
Resting systolic blood pressure (mmHg)	140 ± 24	155 ± 26
Resting ankle brachial index	1.06 ± 9	0.67 ± 20
Total exercise walking distance (meters)	253 ± 95	218 ± 98
Exercise systolic blood pressure (mmHg)	156 ± 30	182 ± 34
Exercised ankle brachial index	1.02 ± 9	0.44 ± 24

Values are means with standard deviations or numbers with percentages.

an increased risk of all cause mortality (Table 2). The cumulative mortality and cardiac death survival curves of both moderate and sever impairment walking distances, shown in figure 1, were significantly worse compared to the no impairment quartile group.

In patients with impaired ABI all impairment total walking distance quartiles were associated with an increased risk of all cause mortality, cardiac death and MACCE, independent of clinical risk factors or exercise ABI (Table 2). The risk of all cause mortality, cardiac death and MACCE increased proportionally when the exercise total walking distance became worse (Table 2). The log rank tests of the cumulative survival of all three impairment walking distance quartiles in the patients with an impaired ABI were significantly worse compared to no impairment total walking distance (Figure 2).

Comparable results were seen for all analyses when repeated at 5 years follow-up. Results did not substantially differ when all analyses were repeated with additional adjustments for date of enrollment, baseline medication use (statins, beta-blockers, ace-inhibitors, aspirin), after excluding patients with baseline diabetes mellitus or with severe ABI impairment (ABI< 0.50).

Table 2. Hazard ratios (HR) with 95% confidence interval (CI) of total walking distance with long-term all cause mortality, cardiac death and major adverse cerebrovascular and cardiac events (MACCE).

Total walking distance		Model I (HR ,95% CI)		Model II (HR ,95% CI)		Model III (HR ,95% CI)	
Patients with normal ABI							
All cause mortality							
I	no impairment	ref		ref		ref	
II	mild impairment	1.70 (0.74	3.89)	1.69 (0.73	3.94)	1.70 (0.73	3.98)
III	moderate impairment	1.52 (0.69	3.39)	1.57 (0.70	3.53)	1.57 (0.70	3.54)
IV	severe impairment	**2.72 (1.24**	**5.98)**	**2.60 (1.17**	**5.80)**	**2.60 (1.16**	**5.78)**
Cardiac death							
I	no impairment	ref		ref		ref	
II	mild impairment	0.82 (0.18	3.67)	1.05 (0.22	5.00)	1.02 (0.21	4.82)
III	moderate impairment	1.29 (0.37	4.54)	1.44 (0.39	5.28)	1.39 (0.38	5.09)
IV	severe impairment	3.00 (0.90	9.89)	2.74 (0.81	9.32)	2.76 (0.82	9.34)
MACCE							
I	no impairment	ref		ref		ref	
II	mild impairment	0.61 (0.24	1.57)	0.75 (0.26	2.02)	0.73 (0.27	2.00)
III	moderate impairment	0.96 (0.41	2.27)	0.88 (0.37	2.07)	0.86 (0.36	2.04)
IV	severe impairment	1.96 (0.87	4.41)	1.63 (0.72	3.73)	1.50 (0.65	3.47)
Patients with impaired ABI							
All cause mortality							
I	no impairment	ref		ref		ref	
II	mild impairment	**133 (1.00**	**1.76)**	*1.27 (0.96*	*1.69)*	*1.26 (0.95*	*1.67)*
III	moderate impairment	**1.62 (1.21**	**2.16)**	**1.56 (1.16**	**2.10)**	**1.52 (1.13**	**2.05)**
IV	severe impairment	**1.83 (1.38**	**2.44)**	**1.73 (1.29**	**2.32)**	**1.69 (1.21**	**2.27)**
Cardiac death							
I	no impairment	ref		ref		ref	
II	mild impairment	1.29 (0.85	1.97)	1.18 (0.77	1.80)	1.16 (0.76	1.77)
III	moderate impairment	**1.66 (1.09**	**2.54)**	**1.62 (1.06**	**2.48)**	**1.55 (1.01**	**2.38)**
IV	severe impairment	**1.91 (1.28**	**2.98)**	**1.73 (1.13**	**2.66)**	**1.67 (1.08**	**2.57)**
MACCE							
I	no impairment	ref		ref		ref	
II	mild impairment	**1.62 (1.62**	**2.25)**	**1.46 (1.05**	**2.03)**	**1.44 (1.03**	**2.00)**
III	moderate impairment	**1.87 (1.87**	**2.60)**	**1.75 (1.25**	**2.45)**	**1.69 (1.20**	**2.37)**
IV	severe impairment	**2.47 (1.77**	**3.44)**	**2.05 (1.46**	**2.88)**	**2.00 (1.41**	**2.80)**

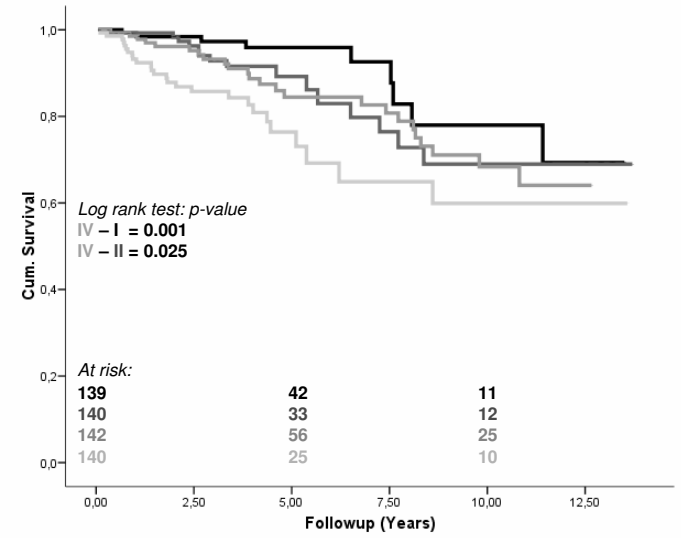
Model I = age and gender

Model II = Model I + current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases and renal failure, resting systolic blood pressure

Model III = Model II + exercise ankle brachial index

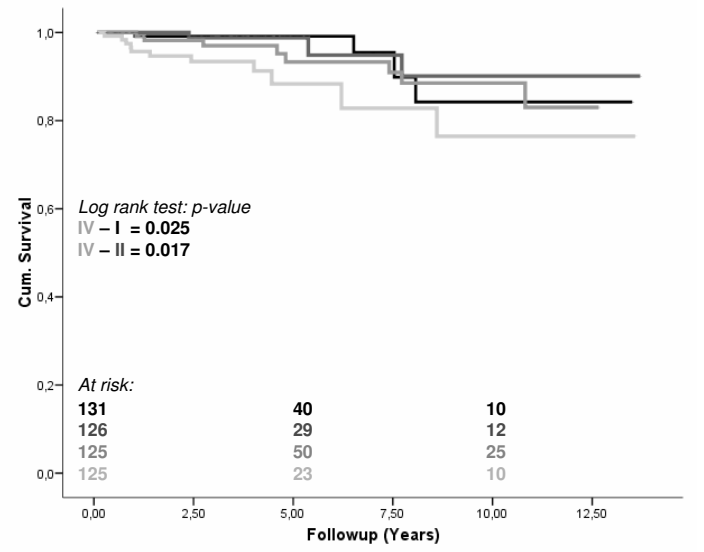
Bold characters are significant values with p-value ≤ 0.05

Figure 1. Survival curves of the four total walking distance quartiles in patients with normal ankle brachial index for long-term all cause mortality and cardiac death.



1a. All Cause Mortality

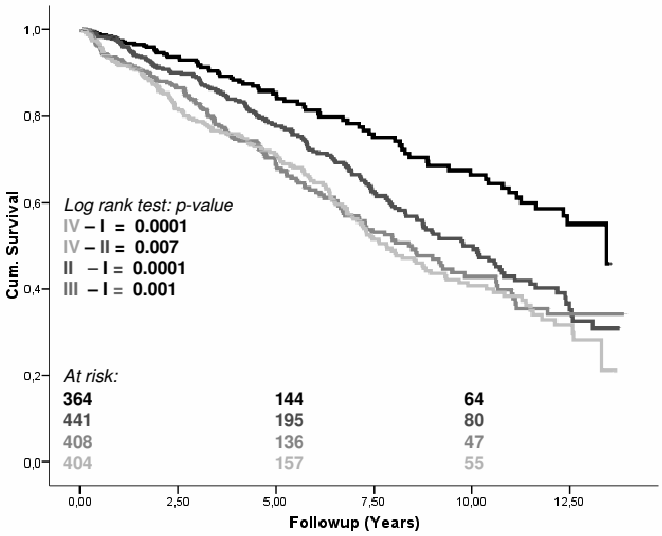
I No impairment in total walking distance
II Mild impairment in total walking distance
III Moderate impairment in total walking distance
IV Severe impairment in total walking distance



1b. Cardiac death

I No impairment in total walking distance
II Mild impairment in total walking distance
III Moderate impairment in total walking distance
IV Severe impairment in total walking distance

Figure 2. Survival curves of the four total walking distance quartiles in patients with impaired ankle brachial index for long-term all cause mortality and cardiac death.



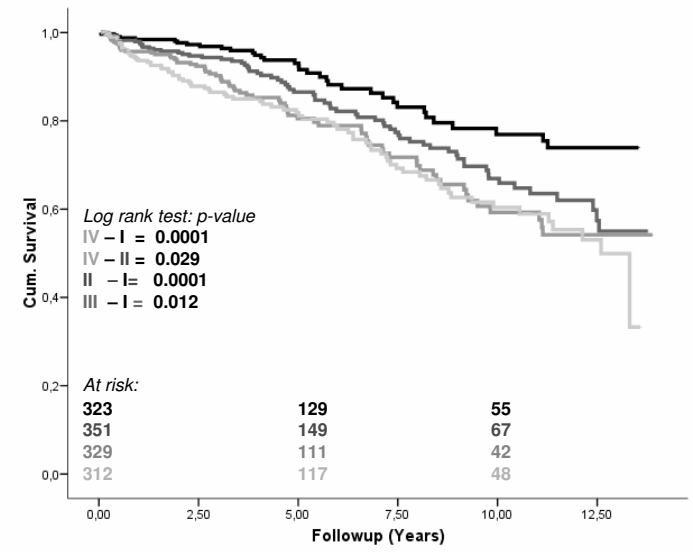
2a. All Cause Mortality

I No impairment in total walking distance

II Mild impairment in total walking distance

III Moderate impairment in total walking distance

IV Severe impairment in total walking distance



2b. Cardiac death

I No impairment in total walking distance

II Mild impairment in total walking distance

III Moderate impairment in total walking distance

IV Severe impairment in total walking distance

DISCUSSION

Our study showed that in patients with a normal resting ABI, a severe impairment in single-stage treadmill exercise total walking distance was associated with a higher mortality rate, independent of other cardiovascular risk factors. In patients with an impaired resting ABI as well, impairment in total walking distance was highly associated with an increased risk of long-term outcome, again independent of other cardiovascular risk factors or ABI.
The ABI is used to assess peripheral arterial stenosis [3]. Values of less then 0.90 are associated with vessel stenosis of more than 50% [2]. Currently, the ABI is commonly used to diagnose or to evaluate PAD [2, 3]. Several studies have found that ABI of < 0.90 is associated with an increased risk of cardiovascular diseases and mortality [4-6]. Furthermore, PAD and low ABI has been associated with a lower level of exercise and physical activity, worse lower-extremity functioning, shorter walking distance on the 6-minute walking test, slower walking velocity and poorer standing balance [8-13]. However, in contrast to the clinical value of the ABI, the clinical value of the walking disability on long-term outcome is unclear, especially in patients with a normal ABI.
In contrast to the results obtained by McDermott et al, we observed that, in 849 patients with a normal resting ABI, a severe impairment in total walking distance was associated with an higher long-term mortality [18]. This difference could be due, as they noted themselves, to their small sample size and short follow-up time (3 till 5 years) [18]. Our results could not be compared with other studies because, as far as we know, no other researches have yet investigated the effects of walking distance in patients with an ABI of ≥ 0.90 on mortality risks.
There are a few possible explanations for this increased risk of long-term mortality in patients with a normal resting ABI. First, it can be hypothesised that these results could be due to diabetic patients in this study group. Patient with diabetes mellitus, although they have an increased risk of cardiovascular morbidity and mortality, are known to have higher ABI [2, 22, 23]. This is thought to be due to seriously calcification of vessels. This results in high vessel wall rigidity and therefore abnormal highly measured systolic blood pressures in the legs, resulting in a high ABI [2, 22, 23]. However, we adjusted for baseline diabetes mellitus in the analyses. In addition, we made additional analyses by excluding patient with baseline diabetes mellitus, which did not substantially change our results. Other confounders such as chronic obstructive pulmonary disease and chronic heart failure could have influenced the results as well. However, we made adjustments in our analyses for these and other potential risk factors. Second, there is a possibility that patients in the normal resting ABI group had PAD, but that it was not reflected by the ABI [24]. It is possible that the cut-off value of 0.90 is not appropriate. Diehm et al. showed that patients with an ABI between 0.90-1.10 had an increased risk of death or major vascular events compared with patients with an ABI of ≥ 1.10 [7]. They state that these patients should be considered

as borderline PAD patients and must be followed closely. The same could be true for our patients, although not reflected by the ABI, these patients have a higher long-term mortality risk.

In patients with an impaired ABI we observed that exercise walking distance was associated with an adverse long-term outcome, independent of other cardiovascular risk factors or ABI. Only a few studies investigated the effects of these impaired physical functioning on long-term outcome in patients with PAD [16-19]. Gardner et al. found that patients with PAD, who performed 1 hour physical activity each week, had a lower mortality risk compared to PAD patients who did not perform physical activity or less than recommended [16]. Their results were comparable with Schiano et al., who observed that self-reported walking speed and walking distance from the Walking Impairment Questionnaire in PAD patients was associated with a higher risk of developing cardiovascular events [19]. However, they did not measure the physical activity objectively, as we did. In addition, both researches had a quite small sample size (434 and 227 patients, respectively) compared tot ours (2191 patients). A third small study in 460 PAD patients found that lower physical activity during daily life, objectively measured by a vertical accelerometer, was associated with a higher mortality, cardiovascular events and cardiovascular death rates [17]. McDermott et al. showed that, comparable to our results, the walking distance in patients with PAD was significantly associated with all cause mortality and cardiovascular death [18].

In conclusion, our study illustrated that walking impairment is a strong independent prognostic indicator of long-term outcome in patients with impaired ABI and in patients with a normal ABI, which should be a warning sign to physicians to monitor these patients carefully and to provide them optimal treatment.

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Exercise ankle brachial index, walking performance and health status in patients with normal and impaired ankle brachial index

7

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ABSTRACT

We investigated the association between exercise ankle brachial index (ABI), walking performance and health status in patients with normal and impaired (ABI). After a mean follow-up of 5 years, 597 patients with known or suspected peripheral artery disease (PAD), who had performed a treadmill exercise test, filled in the 36-item Short-Form Health Survey (SF-36). The study population was divided into 2 groups: patients with a resting ABI (≥ 0.90) and patients with an impaired resting ABI (<0.90). In patients with a normal resting ABI, the exercise ABI was divided into 4 groups (exercise ABI 1.10-1.29, 1.00-1.09, 0.90-0.99 and < 0.90). In patients with an impaired resting ABI the exercise ABI was divided into three groups (0.70-0.9, 0.40-0.69 and < 0.40). The walking distance was divided into quartiles. The SF-36 was used as mean scores and dichotomised into tertiles, indicating the lowest tertile as an impaired health status.

The exercise ABI was associated with physical functioning, but only in patients with a normal resting ABI. On the contrary, the walking distance was significantly associated with all sub-domains, except for mental health, with clear dose-response relationships (p trend < 0.05) in both patient groups. In both groups, an impaired walking distance was strongly related with impairment in physical health.

In conclusion, exercise ABI at a single-stage exercise test was associated with physical functioning, but only in patients with an normal resting ABI. In contrast, the walking distance at an treadmill exercise test was strongly associated with physical health status, in both patients with normal and impaired ABI.

INTRODUCTION

The ankle brachial index (ABI), defined as the ratio between the ankle and brachial systolic blood pressure, is used to diagnose or to evaluate peripheral arterial disease (PAD) [1, 2]. Several studies has shown that ABI is an independent risk factor for cardiovascular diseases and mortality [2-5]. According to the guidelines, a resting ankle brachial index < 0.90 is defined as PAD [2-4]. Recent publications showed that resting ABI values between 0.90 - 1.10 are already associated with a higher mortality and impairment in physical performance, compared to patients with a resting ABI between 1.10-1.30 [5-8].
In addition, PAD patients experience significant limitations in their physical functioning and walking in particular [6-8]. Although several studies have shown that patients with PAD have a decreased quality of life compared to non-PAD patients, most studies didn't observe any or only limited association between the resting ABI and impaired quality of life [9-18]. However, the association between exercise ABI and quality of life, as far as we know, have not been investigated yet. In addition, the relationship between the walking distance on a treadmill exercise test and quality of life is still not completely clear, especially not in patients with a normal resting ABI.
Therefore, we investigated the association between exercise ABI, walking distance and health status in patients with normal and impaired resting ABI.

METHODS

Study Population

Our study population consisted of consecutive enrolment of 1005 patients, who were referred by general practitioners or physicians to the vascular laboratory of the Erasmus Medical Centre, Rotterdam, the Netherlands, for a single-stage treadmill exercise test, between 2003 and 2006. Patients were referred by physicians to diagnose PAD, based on their presenting symptoms. Or patients, who already had a history of intermittent claudication or other symptoms of arterial insufficiency, were sent to evaluate their PAD. Excluded were patients who were not able to perform the treadmill exercise test.

Single-stage treadmill exercise test

Specialised trained personnel supervised the exercise tests, using a prescribed protocol. Details on the protocol have been previously reported [19, 20]. Briefly, the systolic blood pressure was measured in supine position after 15 minutes rest. In addition, the blood pressure at the dorsalis pedis and posterial tibial arteries were measured at both sides. Then, all patients were asked to walk on a treadmill with a speed of 4 km/h for a maximum of 5 minutes. No inclining plane or graded inclines were used. Total walking distance was

recorded. Immediately after the exercise the systolic blood pressure at the arm, as well as at the dorsalis pedis or posterial tibial artery, depending which one was highest at rest, were measured in supine position. ABI at rest and after the exercise test were calculated by dividing the highest systolic blood pressure at the dorsalis pedis or posterial tibial arteries by the highest systolic blood pressure at the arm. The lowest measured ABI was used in the analyses.

Covariate assessment

Demographic and clinical information were collected from the medical records. The following definitions were used for the different covariates. Diabetes mellitus was documented when patients presented with the diagnosis, made by the referred physician, required anti-diabetic medication, having a fasting glucose level ≥ 126mg/dl, a glucose level of ≥ 200mg/dl after a oral glucose tolerance test or plasma non-fasting glucose levels of ≥ 200mg/dl [21, 22]. Hypertension was recorded if a patient had a blood pressure > 140/90mmHg or received with antihypertensive medication. Chronic obstructive pulmonary disease was classified as a history of chronic obstructive pulmonary disease or pulmonary medication use. Hypercholesterolemia was noted when patients presented with a history of hypercholesterolemia in their chart or received lipid-lowering medication or a plasma cholesterol level of 212mg/dl or more. Renal dysfunction was defined as having a serum creatinine level of ≥2.0 mg/dl or receiving dialyses.

Health status

To all patients, in 2006 the Dutch version of the 36-item Short-Form Health Survey (SF-36) were sent. The SF-36 is one of the most widely used generic health status measurements developed in the United States as a part of the Medical Outcomes Study [23]. The Dutch version of the 36-item Short Form Health Survey (SF-36) was used to evaluate eight domains of health status: physical functioning, role limitation due to physical health problems, social functioning, role limitations due to emotional problems, mental health, vitality, bodily pain, general health. All scores were converted to a scale from 0 to 100, using a standardised protocol, with lower scores indicating lower health status. In total 126 patients had died and 597 returned the questionnaires (response rate 71%).

Statistical methods

Patients were divided into two groups: (1) Patients with a normal ABI with a resting ABI ≥ 0.90 and (2) patients with an impaired ABI with a resting ABI < 0.90. Following these criteria, 309 patients (52%) were considered as having an impaired ABI.

In patients with a resting ABI ≥ 0.90, the exercise ABI was divided into four groups, namely: exercise ABI 1.10-1.29 (group I, reference group), 1.00-1.09 (group II), 0.90-0.99 (group III), < 0.90 (group IV).

In patients with an impaired resting ABI, the exercise ABI was divided into three groups, ABI 0.70-0.89 (group I), ABI 0.40-0.69 (group II) and ABI < 0.40 (group III).
The total walking distance was categorised into quartiles (no (reference), mild, moderate, severe walking impairment).
To identify differences in baseline characteristics between responders and non-responders of the SF-36 questionnaire, student's t- tests for continuous variables and chi-square tests for categorical variables were used. To compare mean differences between the exercise ABI, total walking distance quartiles and SF-36 eight sub-domains, ANOVA was used with adjustments for potential clinical risk factors; age, gender, current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases (consisted of angina pectoris, myocardial infarction or coronary artery revascularisation), renal failure, time between the exercise test and SF-36 form, resting systolic blood pressure an exercise ABI. The dose-response relationship was investigated with p for trend calculated using linear-by-linear association. Additionally, all eight sub-domains of the SF-36 were dichotomized into tertiles, representing the lowest tertile as an impaired heath status, making the interpretation for clinical practise more clearly [24]. Logistic regression analyses was used to identify the association between the exercise ABI, total walking distance and impaired health status, with adjustments for similar potential clinical risk factors. For all tests significance was defined as a p-value of ≤ 0.05. Analyses were performed in SPSS 15 for windows.

RESULTS

The responders and non-responders of the SF-36 questionnaire were comparable for baseline characteristics, exept for COPD (responders 11%, non-responders 17%). The responding patients had answered the SF-36 form well, with low rates of missing values for individual items (ranging from 0,8% till 6%), comparable to other Dutch populations [23]. Baseline characteristics of both patient groups (normal and impaired resting ABI) are shown in Table 1.

Normal resting ABI

In patients with a normal resting ABI, a dose-response relationship (p trend < 0.05) was observed between the exercise ABI and physical functioning, social functioning, vitality and general health (Figure 1). Patients with an exercise ABI < 0.90 had a significant lower mean score in physical functioning compared to patients with an exercise ABI between 1.10-1.29 (p-value 0.014, figure 1). In the logistic regression analyses, in which all eight sub-domains of the SF-36 were dichotomized into tertiles representing the lowest tertile

Table 1 Baseline characteristics in patients with normal or impaired resting ankle brachial index (ABI).

Characteristics	Patients with normal ABI (n=288)	Patients with impaired ABI (n=309)	P-value
Age (years)	**59 ± 14**	**63 ± 12**	**0.01**
Body mass index (kg/m^2)	27 ± 5	28 ± 16	0.3
Male (%)	167 (58)	194 (62)	0.2
Chronic obstructive pulmonary disease (%)	31 (11)	32 (11)	1.0
Hypertension (%)	**96 (34)**	**132 (44)**	**0.01**
Diabetes mellitus (%)	61 (21)	78 (26)	0.2
Smoking (%)	**88 (31)**	**123 (41)**	**0.01**
Hypercholesterolemia (%)	90 (32)	1115 (38)	0.09
Renal failure (%)	22 (8)	28 (9)	0.5
History of cardiac disease (%)	76 (27)	89 (29)	0.5
History of heart failure (%)	13 (5)	15 (5)	0.8
Exercise test:			
Resting ankle brachial index	**1.04 ± 9**	**0.62 ± 15**	**0.01**
Total exercise walking distance (meters)	**262 ± 987**	**215 ± 97**	**0.01**
Exercised ankle brachial index	**0.93 ± 19**	**0.39 ± 21**	**0.01**

Values are means with standard deviations or numbers with percentages.

as an impaired heath status, none of the exercise ABI groups were significantly associated with an impaired health status (table 2).

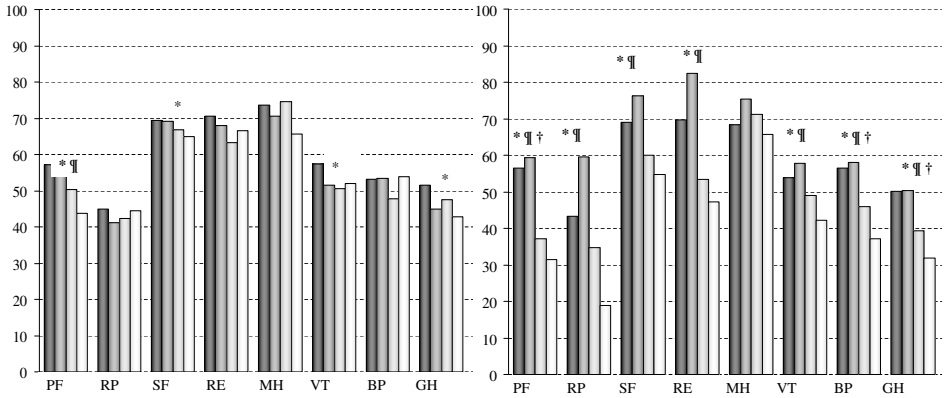
The total walking distance was significant (p trend < 0.05) associated with health status for all sub-domains, except for mental health (Figure 1). With decreasing walking distance health status became more impaired, indicating a dose-response relationship (Figure 1). Moderate and severe walking distance impairment were associated with an impairment in physical functioning, bodily pain and general health (Table 2). Severe impaired walking distance was associated with an impaired health status in role limitations due to physical health problems, social functioning, role limitations due to emotional problems and vitality, compared to patients with no impairment in total walking distance (Table 2).

Impaired resting ABI

In patients with an impaired resting ABI, none of the exercise ABI was associated with one of the eight sub-domains of the SF-36 (Figure 2). In addition, no association between exercise ABI and impaired health status was observed (Table 3).

This was in contrast with the total walking distance. Walking distance was significantly associated with health status at all SF-36 sub-domains, except for mental health (Figure 2). Again, an evident dose-response relationship was observed (Figure 2). Patients with severe and moderate walking distance impairment had a significant lower mean score in physical functioning, vitality and bodily pain compared to patients with no impairment in

Figure 1. Mean scores on the SF-36 eight sub-domains in patients with a normal resting ankle brachial index (ABI).



1.a Exercise ankle brachial index

I 1.10-1.29

II 1.00-1.09

III 0.90-0.979

IV <0.90

1b. Total walking distance quartiles

I No impairment

II Mild impairment

III Moderate impairment

IV Severe impairment

Physical functioning (PF). role limitation due to physical health problems (RP). social functioning (SF). role limitations due to emotional problems (RE). mental health (MH). vitality (VT). bodily pain (BP). general health (GH).

P trend* = p-value <0.05

P-value for differences in mean scores between no and severe impairment (ANOVA) ¶ = p-value <0.05

P-value for differences in mean scores between no and moderate impairment (ANOVA) † = p-value <0.05

total walking distance (Figure 2). Role limitation due to physical health problems, social functioning and general health was associated with severe walking distance impairment (Figure 2). Moderate and severe decreased walking distances were significantly associated with an impaired physical functioning, and bodily pain (Table 3). A severe decreased walking distance was related with an impaired role limitation due to physical health problems, social functioning and general health (Table 3).

DISCUSSION

Our study showed that the exercise ABI at a single-stage exercise test was associated with physical functioning, but only in patients with a normal resting ABI. The total walking distance was strongly associated with all physical subdomains of health status with evident dose-response relationships, in both patients with normal and impaired resting ABI.

PAD has been associated with a lower level of exercise, physical activity, worse lower-extremity functioning, shorter walking distance and slower walking velocity [6-8, 25]. Previously, researchers observed an impaired quality of life in patient with PAD compared to non-PAD

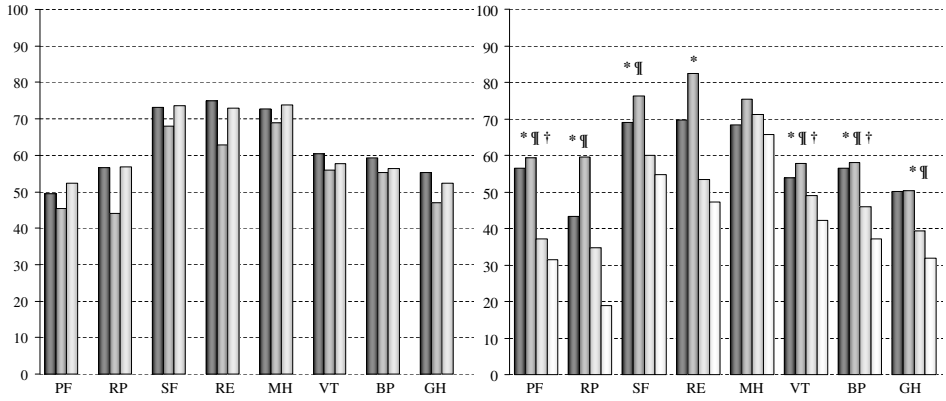
Table 2 Logistic regression analyses between an impaired health status, exercise ABI and total walking distance in patients with normal resting ABI.

Patients with normal ABI	Physical functioning	Role limitation due to physical health problems	Social functioning	Role limitations due to emotional problems	Mental health	Vitality	Bodily pain	General health
	OR 95%CI	OR 95%CI	OR 95%CI	OR 95%CI	OR 95%CI	OR 95%CI	OR 95%CI	OR 95%CI
Exercise ABI *								
I 1.10-1.29	ref	ref	ref	ref	ref	ref	ref	ref
II 1.00-1.09	1.18 (0.42- 3.30)	1.11 (0.47- 2.63)	1.10 (0.46- 2.62)	0.84 (0.33- 2.13)	1.25 (0.51-3.08)	1.45 (0.59-3.59)	1.20 (0.51-2.82)	1.48 (0.59- 3.75)
III 0.90-0.99	1.55 (0.50-4.88)	0.79 (0.29-2.16)	1.16 (0.43- 3.13)	1.06 (0.37- 3.03)	0.75 (0.26-2.22)	2.36 (0.85- 6.54)	0.83 (0.31-2.26)	1.00 (0.34- 2.94)
IV <0.90	1.86 (0.67- 5.19)	0.94 (0.38- 2.32)	1.41 (0.57- 3.50)	1.04 (0.41-2.68)	1.99 (0.79- 5.00(	1.28 (0.50-3.27)	1.11 (0.45- 2.72)	1.26 (0.47-3.34)
Total walking distance¶								
I no impairment	ref	ref	ref	ref	ref	ref	ref	ref
II mild	0.62 (0.24-1.63)	0.46 (0.20-1.02)	0.67 (0.31-1.43)	0.50 (0.20-1.21)	0.33 (0.14-0.80)	0.69 (0.31-1.50)	1.02 (0.48-2.15)	0.92 (0.41-2.08)
III moderate	**5.10 (2.10-12.39)**	1.66 (0.71-3.85)	1.83 (0.78-4.32)	2.17 (0.91-5.81)	0.69 (0.28-1.67)	1.77 (0.75-4.17)	**2.36 (1.00-5.57)**	1.961 (0.80-4.79)
IV severe	**8.06 (2.68-24.29)**	**4.09 (1.34-12.50)**	**4.39 (1.48-13.06)**	**3.16 (1.10-9.12)**	0.79 (0.28-2.22)	**3.42 (1.21-9.68)**	**4.73 (1.60-13.96)**	**8.09 (2.34-27.92)**

* Logistic regression analyses, adjusted for: age, gender, current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, renal failure, time between exercise test and SF-36 and * **walking distance OR ¶ exercise ankle brachial index**

Bold characters are significant (p-value ≤ 0.05)

Figure 2. Mean scores on the SF-36 eight sub-domains in patients with an impaired resting ankle brachial index (ABI).



2a Exercise ankle brachial index
I 0.70-0.89
II 0.40-0.69
III <0.40

2b. Total walking distance
I No impairment
II Mild impairment
III Moderate impairment
IV Severe impairment

Physical functioning (PF). role limitation due to physical health problems (RP). social functioning (SF). role limitations due to emotional problems (RE). mental health (MH). vitality (VT). bodily pain (BP). general health (GH).
P trend* = p-value <0.05
P-value for differences in mean scores between no and severe impairment (ANOVA) ¶ = p-value <0.05
P-value for differences in mean scores between no and moderate impairment (ANOVA) † = p-value <0.05

control groups [11, 12]. Several studies which evaluated the association of the ABI and quality of life in patients with PAD found no or only limited association between ABI and health status [13, 14, 16-18]. These studies investigated only the relationship between the resting ABI and health status. As far as we know no studies investigated the relationship between exercise ABI and health status in both patient with impaired and normal resting ABI. In the present study we also observed a limited association between the exercise ABI and health status. We found only an association between physical functioning and exercise ABI in only patients with a normal resting ABI.

On the contrary, we observed a strong relationship between walking distance at a single-stage exercise test and SF-36 in both patients with a normal and an impaired resting ABI. As far as we know, no other studies investigated the association between walking distance and health status in patients with a normal resting ABI before. We previously demonstrated that patients with a normal ABI and a severe walking impairment had an increased risk of all cause mortality and cardiac death [20]. In the present study we additionally showed that in this patient group impairment in total walking distance was also associated with an impairment in physical health status. Diehm et al. showed that patients with an ABI between 0.90-1.10 had already an increased risk of death or major vascular events compared to patients with an ABI of ≥ 1.10 [4].

Table 3 Logistic regression analyses between an impaired health status, exercise ABI and total walking distance in patients with impaired resting ABI.

Patients with impaired ABI	Physical functioning	Role limitation due to physical health problems	Social functioning	Role limitations due to emotional problems	Mental health	Vitality	Bodily pain	General health
	OR 95%CI	OR 95%CI	OR 95%CI	OR 95%CI	OR 95%CI	OR 95%CI	OR 95%CI	OR 95%CI
Exercise ABI *								
I 0.70-0.89	ref	ref	ref	ref	ref	ref	ref	ref
II 0.40-0.69	1.61 (0.44- 5.90)	2.26 (0.53-9.69)	1.31 (0.40-4.29)	2.05 (0.49- 8.69)	0.82 (0.25- 2.70)	1.75 (0.47- 6.48)	1.06 (0.32- 3.51)	1.79 (0.51- 6.28)
III <0.40	0.72 (0.20- 2.53)	1.25 (0.30- 5.23)	1.19 (0.38- 3.71)	1.20 (0.29- 4.94)	0.46 (0.14- 1.47)	0.99 (0.27- 3.57)	0.91 (0.29- 2.88)	1.04 (0.31- 3.49)
Total walking distance¶								
I no impairment	ref	ref	ref	ref	ref	ref	ref	ref
II mild	2.37 (0.72-7.79)	0.89 (0.33-2.43)	1.00 (0.42-2.40)	0.73 (0.28-1.92)	1.85 (0.75-4.54)	1.25 (0.50-3.14)	1.02 (0.40-2.58)	0.90 (0.35-2.30)
III moderate	**5.46 (1.79-16.64)**	1.70 (0.68-4.25)	1.60 (0.71-3.60)	0.98 (0.40-2.44)	1.51 (0.62-3.66)	2.17 (0.91-5.16)	**2.76 (1.17-6.51)**	1.74 (0.73-4.17)
IV severe	**7.70 (2.46-24.12)**	**2.94 (1.17-7.40)**	**2.77 (1.20-6.41)**	1.49 (0.60-3.69)	1.23 (0.49-3.08)	1.95 (0.80-4.77)	**2.58 (1.07-6.25)**	**2.55 (1.04-6.24)**

* Logistic regression analyses, adjusted for: age, gender, current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, renal failure, time between exercise test and SF-36 and * **walking distance OR ¶ exercise ankle brachial index**

Bold characters are significant (p-value ≤ 0.05)

They state that these patients should be considered as borderline PAD patients and must be followed closely, which was also confirmed by a resent editorial comment [26]. The same could be true for our patients. These patients probably have borderline PAD. The walking distance at the treadmill exercise test in these patient category is of important prognostic value for long-term outcome and, as shown in this study, is also strongly associated with an impairment in health status [20].

In patients with an impaired ABI, two previous studies has shown that an impaired resting ABI walking distance was associated with an increased risk in all cause mortality and cardiac death [20, 27]. A few studies investigated the relation between walking performance and quality of life in PAD patients [12, 15, 18]. Myers et al. for example detected a significant relation between total walking distance, physical functioning and vitality. In contrast, we observed associations with all physical sub-domains of the SF-36, except mental health, with evident dose-response relationships.

Despite the large study population, there are some limitations to report. The SF-36 health survey is one of the most commonly used questionnaires to measure health status in PAD patients and it is proposed to be used as a standardised measurement of health status [28, 29]. However, disease specific questionnaires are better in discriminating differences within disease specific populations [28-30]. Therefore, it is recommended to use not only the SF-36 but also a disease specific questionnaire [28-30]. Unfortunately, because the Dutch version of the disease specific questionnaire the Peripheral Artery Questionnaire (PAQ) had to be validated first, we were not able yet to use the disease specific questionnaire. Furthermore, we had only SF-36 scores at one time point and thus, we were not able to investigate the association between walking distance and change of heath status over time.

In conclusion, exercise ABI at a single-stage exercise test was associated with physical functioning, but only in patients with an normal resting ABI. In contrast, an impaired walking distance at a treadmill exercise test was strongly associated with all physical subdomains of health status with evident dose-response relationships, in both patients with normal and impaired resting ABI, and could be a warning sign to physicians to monitor these patients carefully.

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A decline in walking distance predicts long-term outcome in patients with known or suspected peripheral artery disease

8

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ABSTRACT

Aim: To assess the predictive value of a decline in total walking distance and ankle brachial index (ABI) on all cause mortality and cardiac death in patients with known or suspected peripheral artery disease (PAD).

Methods: 261 patients, who performed two times a single-stage treadmill walking test to evaluate their PAD, were enrolled in an observational study. Patients who underwent surgery during follow-up were excluded. Delta total walking distance and delta resting and exercise ABI consisted of the difference between the first and the second test. All three variables were categorised into two groups, stable / improvement or a decline.

Results: The mean follow-up was 6 years. At both 5 years and total follow-up time, a decline in total walking distance was independent and highly associated with an increased mortality risk and cardiac death (HR 2.31, 95% CI [1.35-3.96], HR 3.55 [95% CI 1.53-8.21], respectively). A decline in resting or exercise ABI was after adjustment for delta walking distance not significantly associated with all cause mortality or cardiac death.

Conclusion: A decline in total walking distance in single-stage treadmill exercise tests is a strong prognostic predictor of all-cause mortality and cardiac death in the short term and long term.

INTRODUCTION

Peripheral arterial disease (PAD) is associated with an increased risk of cardiovascular morbidity and mortality [1, 2]. To diagnose or to evaluate PAD, the ankle brachial index (ABI), the ratio between the ankle and brachial systolic blood pressure, is used [2, 3]. Several studies have shown that ABI is an independent risk factor for cardiovascular diseases and mortality [1, 2, 4-8]. Patients with PAD, due to the impaired circulation, experience significant limitation in physical functioning and walking in particular [7, 9-13]. However, no studies have yet been preformed to assess the predictive value of a decline in walking performance on long-term all cause mortality and cardiac death. Besides, hardly any researches have investigated the effects of a decline in resting ABI and exercise ABI and long-term outcome [14].

Therefore, to bridge these knowledge gaps, we investigated the predictive value of a decline in walking distance or ABI at single-stage exercise treadmill tests on all cause mortality and cardiac death in patients with known or suspected PAD.

METHODS

Study Population

Our study population consisted of 261 patients, who were referred by general practitioners or physicians to the vascular laboratory of the Erasmus Medical Centre, Rotterdam, the Netherlands, for a single-stage treadmill exercise test, between 1993 and 2006. Our study population is a representative population of daily clinical practice in a vascular laboratory. Patients were referred by physicians to diagnose PAD, based on their presenting symptoms. Or patients, who already had a history of intermittent claudication or other symptoms of arterial insufficiency, were sent to evaluate their PAD. All patients performed two times a single-stage treadmill walking test to evaluate PAD, with a median interval of 7 months and a mean interval of one year (± sd 0.96). Additionally, patients who underwent vascular surgery between the two measurements were excluded.

Single-stage exercise test

Specialised trained personnel supervised the exercise tests, using a prescribed protocol. The systolic blood pressure was measured with a blood pressure device (Maxi stable 3, presso stabl; Welch Allyn Inc, Skaneateles Falls, New York, USA) at both left and right arms in supine position after 15 minutes rest. In addition, the blood pressure at the dorsalis pedis and posterior tibial arteries were measured at both sides, using a Doppler ultrasonic instrument with a 8-MHZ vascular probe (Imexdop CT+ vascular Doppler; Miami Medical, GlenAllen, Va). After these measurements all patients were asked to walk on a treadmill

with a speed of 4 km/h for a maximum of 5 minutes. No inclining plane or graded inclines were used. During the walking test patients were ask to tell the personnel when they started to feel pain in the legs. Patients were encouraged to finish the whole test. Time and walking distance till the occurrence of leg pain and the total walking time and distance were recorded. Immediately after the exercise, the systolic blood pressure level in the arm, and in the dorsalis pedis or posterior tibial arteries, depending on which one was highest at rest, was measured in a supine position. ABI at rest and after the exercise test were calculated by dividing the systolic blood pressure at the dorsalis pedis or posterial tibial arteries, depending which one was the highest, by the highest systolic blood pressure at the arm. For the resting ABI the interobserver and intraobserver agreement was 97% and 98%, and for the exercise ABI 96% and 97% [5]. All variables were incorporated in a computerised hospital database.

Covariate assessment

From the medical records, the following baseline characteristics were collected: age, gender, current smoking, diabetes mellitus, hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, renal dysfunction, history of congestive heart failure, history of cardiac disease consisted of angina pectoris, myocardial infarction or coronary artery revascularisation. The following definitions were used for the different covariates. Diabetes mellitus was documented when patients having a fasting glucose level ≥126mg/dl, a glucose level of ≥200mg/dl after an oral glucose tolerance test, a plasma nonfasting glucose levels of ≥200mg/dl, or were using already antidiabetic medication at baseline [15,16]. Hypertension was recorded if a patient had a blood pressure higher > 140/90mmHg or treated with antihypertensive medication. Chronic obstructive pulmonary disease was classified as a history of chronic obstructive pulmonary disease or pulmonary medication use. Hypercholesterolemia was noted when patients presented with the diagnosis, made by the referred physician or received lipid-lowering medication. Renal dysfunction was defined as having a serum creatinine level of ≥2.0 mg/dl or receiving dialyses.

Follow-up

The follow-up vital status, which was obtained by reviewing the civil registries, was completed for all patients. The cause of death was obtained from the Central Bureau of Statistics or from medical records. Cardiac death was defined as death of cardiac origin caused by myocardial infarction, cardiac arrhythmias or congestive heart failure. Of 12 patients no course of death could be traced.

Statistical methods

The delta total walking distance was computed from the difference between the first and the second total walking distance of the single-stage treadmill exercise test. The resting

and exercise delta ABI was calculated by subtracting the lowest measured ABI in rest or after exercise of the first exercise test from the lowest measured ABI at rest or after exercise of the second exercise test. All three variables were categorised into two groups, stable / improvement or a decline. To identify differences in baseline characteristics between the two groups of delta total walking distance, student's t- tests for continuous variables were used and chi-square tests for categorical variables. Cox proportional hazard ratio's (HR) with 95% confidence interval (95% CI) at 5 year and total follow-up time were calculated to define the relationship between the delta total walking distance, delta resting ABI, delta exercise ABI and all cause long-term mortality and cardiac death. Proportionality of hazards was tested graphically based on visual inspection of log-log survival curves. Adjustments were made for potential clinical risk factors. Besides, to calculate only the association of the delta walking distance or the delta resting of exercise ABI we including total walking distance at the first and the second test or ABI at the first and the second test into the models. Additional analyses with adjustments for time between the two tests and interaction terms for the first total walking distance with delta walking distance and the first ABI with delta ABI were made. Besides, we investigated if there were correlations with delta walking distance and baseline resting or exercise ABI using linear regression analyses. The Kaplan Meier method with log-rank tests at 5 year and total follow-up time, was used to compare survival of the two groups of delta total walking distance, delta resting and exercise ABI. For all test significance was defined as a p-value of ≤ 0.05. Analyses were performed in SPSS 14 for windows.

RESULTS

Mean age was 61 years and 62% were men. Of the total population 48% showed a decline in the total walking distance and 33% in resting or exercise ABI. Patients with a decline in the total walking distance had less often hypertension at baseline and both the resting and exercise ABI of the first test was higher (Table 1). In 56% of the patients with a decline in total walking distance, this walking distance decline was not reflected by a decline in ABI (Table 1).

The mean follow-up period was 6 years, ranging from 6 month to 14 years. During the follow-up period, 19% in the group with stable or improved total walking distance died whereof 35% were of cardiac origin. In the group with a decline in total walking distance 34% died, whereof 52% were of cardiac origin. The log-log survival curves to test the proportionality of hazards did not show interactions with time and no correlations were observed between delta walking distance, resting or exercise ABI. A decline in total walking distance was significantly associated with an increased risk of all cause mortality at 5 years and total follow-up time, independently of clinical risk factors, delta exercise ABI,

Table 1. Baseline characteristics in patients with stable or improvement in total walking distance and patients with a decline in total walking distance.

Characteristics	Stable or improvement in total walking distance (n = 136)	Decline in total walking distance (n = 125)	p-value
Age (years)	62 ± 12	61 ± 12	0.4
Body mass index (kg/m^2)	26 ± 4	26 ± 4	1.0
Male (%)	79 (58)	85 (68)	0.1
Chronic obstructive pulmonary disease (%)	12 (9)	17 (14)	0.2
Hypertension (%)	**60 (44)**	**35 (28)**	**0.007**
Diabetes mellitus (%)	33 (24)	26 (21)	0.5
Smoking (%)	49 (36)	55 (44)	0.2
Hypercholesterolemia (%)	38 (27)	33 (26)	0.8
Renal failure (%)	6 (4)	8 (6)	0.5
History of cardiac disease (%)	36 (27)	45 (36)	0.1
History of heart failure	9 (7)	5 (4)	0.3
First exercise test:			
Resting ankle brachial index	**0.68 ± 0.20**	**0.75 ± 0.19**	**0.007**
Total exercise walking distance (meters)	**222 ± 96**	**247 ± 96**	**0.004**
Exercised ankle brachial index	**0.44 ± 0.26**	**0.53 ± 0.27**	**0.009**
Second exercise test:			
Resting ankle brachial index	0.77 ± 0.22	0.73 ± 0.22	0.1
Total exercise walking distance (meters)	**263 ± 82**	**195 ± 115**	**0.001**
Exercised ankle brachial index	0.57 ± 0.29	0.51 ± 0.32	0.09
Decline in resting ankle brachial index (%)	**30 (22)**	**55 (44)**	**0.001**
Decline in exercise ankle brachial index (%)	**31 (23)**	**55 (44)**	**0.001**

Values are means with standard deviations or numbers with percentages.
Bold characteristics are significant with p-values ≤ 0.05

time between the two tests, interaction terms or walking distance at the first or second test (Table 2). Cardiac death at 5 years and total follow-up was significantly associated with a decline in the total walking distance as well (Table 2). After adjustment for baseline characteristics, a decline in resting or exercise ABI was significantly associated with all cause mortality at 5 years follow-up (Table 2). However, after including the delta total walking distance into the model, the significant results of both a decline in resting and exercise ABI disappeared (Table2). Cardiac death was not associated with a decline in resting or exercise ABI (Table 2).

The cumulative survival of all cause mortality and cardiac death at 5 year and total follow-up time in the decline in total walking distance group was significantly worse compared to the stable or improved total walking distance group (Figure1 and figure 2). The log rank tests of the survival curves on all cause morality in the decline in resting or exercise ABI

Table 2. Hazard ratios (HR) with 95% confidence interval (CI) of delta total walking distance, resting ankle brachial index or exercise ankle brachial index (ABI) on all cause mortality and cardiac death at 5 years and total follow-up.

All cause mortality	Model I (HR ,95% CI)	Model II (HR ,95% CI)	Model III (HR ,95% CI)	Model IV (HR ,95% CI)
Total walking distance				
Stable or improved	1.00	1.00 [a]	1.00 [c]	1.00 [f]
5 years; declined	**3.50 (1.73 - 7.06)**	**3.09 (1.46 - 6.50)**	**3.13 (1.37 - 7.16)**	**3.42 (1.39 - 8.39)**
Total; declined	**2.31 (1.35 - 3.96)**	**2.15 (1.21 - 3.70)**	**2.44 (1.30 - 4.60)**	**2.54 (1.27 - 5.08)**
Resting ABI				
Stable or improved	1.00	1.00[b]	1.00 [d]	1.00 [g]
5 years; declined	**2.29 (1.23 - 4.26)**	1.62 (0.84 - 3.12)	0.79 (0.35 - 1.78)	0.95 (0.41 - 2.20)
Total; declined	**1.73 (1.02 - 2.91)**	1.58 (0.93 - 2.70)	0.89 (0.44 - 1.79)	1.05 (0.51 - 2.17)
E*xercise ABI*				
Stable or improved	1.00	1.00 [b]	1.00 [e]	1.00 [h]
5 years; declined	**1.98 (1.06 - 3.70)**	1.48 (0.75 - 2.89)	1.19 (0.53 - 2. 68)	1.39 (0.57 - 3.37)
Total; declined	1.38 (0.82 - 2.33)	1.21 (0.69 - 2.10)	1.08 (0.56 - 2.10)	0.96 (0.47 - 1.96)
Cardiac death	Model I (HR ,95% CI)	Model II (HR ,95% CI)	Model III (HR ,95% CI)	Model IV (HR ,95% CI)
Total walking distance				
Stable or improved	1.00	1.00 [a]	1.00 [c]	1.00 [f]
5 years; declined	**4.72 (1.63 - 13.70)**	**4.12 (1.33 - 12.80)**	**4.26 (1.20 - 15.15)**	**4.73 (1.23 - 18.25)**
Total; declined	**3.55 (1.53 - 8.21)**	**3.14 (1.27 - 7.80)**	**3.41 (1.28 - 9.05)**	**3.40 (1.18 - 9.81)**
R*esting ABI*				
Stable or improved	1.00	1.00 [b]	1.00 [d]	1.00 [g]
5 years; declined	2.21 (0.84 - 5.81)	1.48 (0.53 - 4.16)	0.38 (0.09 - 1.56)	0.43 (0.11 - 1.68)
Total; declined	2.18 (0.93 - 5.10)	1.98 (0.83 - 4.76)	0.75 (0.24 - 2.38)	0.73 (0.22 - 2.45)
Exercise ABI				
Stable or improved	1.00	1.00 [b]	1.00 [e]	1.00 [h]
5 years; declined	1.83 (0.75 - 4.45)	1.15 (0.44 - 2.99)	0.96 (0.30 - 3.08)	0.86 (0.24 - 3.07)
Total; declined	2.18 (0.93 - 5.10)	1.36 (0.59 - 3.13)	1.40 (0.54 - 3.61)	1.08 (0.38 - 3.06)

Model I: age, sex, current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, renal failure, and systolic blood pressure at rest.

[a]Model II: Model I + change in **exercise ABI**

[b]Model II: Model I + delta **total walking distance**.

[c]Model III: Model II + time between the tests + interaction terms for **total walking distance** at test 1 with delta walking distance

[d]Model III: Model II + time between the tests + interaction terms for **resting ABI** at test 1 with delta resting ABI

[e]Model III: Model II + time between the tests + interaction terms for **exercise ABI** at test 1with delta exercise ABI.

[f]Model IV: Model II + **walking distance** at test 1 and walking distance at test 2

[g]Model IV: Model II + **resting ABI** at test 1 and resting ABI at test 2

[h]Model IV: Model II + **exercise ABI** at test 1 and exercise ABI at test 2.

group was significantly worse compared to the stable or improved ABI group, but only at 5 years follow-up (Figure 1). The survival curves of cardiac death at 5 years and total follow-up was significantly worse for patients with a decline in exercise ABI, but not for a patients with a decline in resting ABI (Figure 2).

DISCUSSION

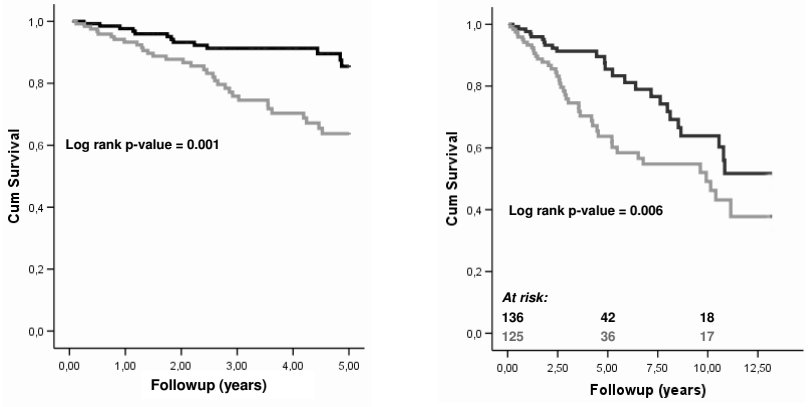
For the first time, we were able to show that a decline in total walking distance at single-stage treadmill exercise tests was highly associated with in increased risk of all cause mortality and cardiac death, independent of clinical risk factors and delta ABI. A decline in resting or exercise ABI was related to an increased risk of all cause mortality, but disappeared when additional adjustments for delta total walking distance were made.

The ABI is used to assess arterial stenosis [3]. Values of less then 0.90 are associated with vessel stenosis of more than 50% [2]. Today, the ABI is commonly used to diagnose or to evaluate PAD [2, 3]. Several studies found that ABI of < 0.90 is associated with an increased risk of cardiovascular diseases and mortality [4-8]. Furthermore, PAD and low ABI has been associated with a lower level of exercise and physical activity, worse lower-extremity functioning, shorter walking distance on the 6-minute walking test [7, 9-13].

Only one study, as far as we know, investigated the effects of a decline in resting ABI and mortality [14]. They observed a significant increased risk for all-cause mortality and cardiovascular mortality at three years follow-up, but not at total follow-up time of six years. However, they did not made adjustments for walking performance, which in our study resulted in a disappearance of the significant association between the ABI and mortality. In addition, they included also patients who underwent surgery between the two tests. Besides, they did not show baseline characteristics and test results for the three delta ABI groups. Therefore, no differences between the groups could be identified. Finally, the effects of a decline in exercise ABI were not investigated. Therefore our results of delta exercise ABI on mortality risks and cardiac death could not be compared.

Mcdermott et al. investigated the association between functional performance and mortality [17]. They observed that an inferior walking distance at a six minute walking test was associated with an increased all cause mortality and cardiovascular mortality in patients with an ABI < 0.90. However, they did not investigate the effects of an altered walking performance on mortality risk. In our study we observed a strong relation between a decline in walking distance and all cause mortality and cardiac death, independent of clinical risk factors and ABI. Even additional adjustments for baseline walking performance and walking performance at the second test did not change the results, indicating that an altered walking distance is an extremely important and independent prognostic factor for long-term outcome. Our results could not be compared with other study results,

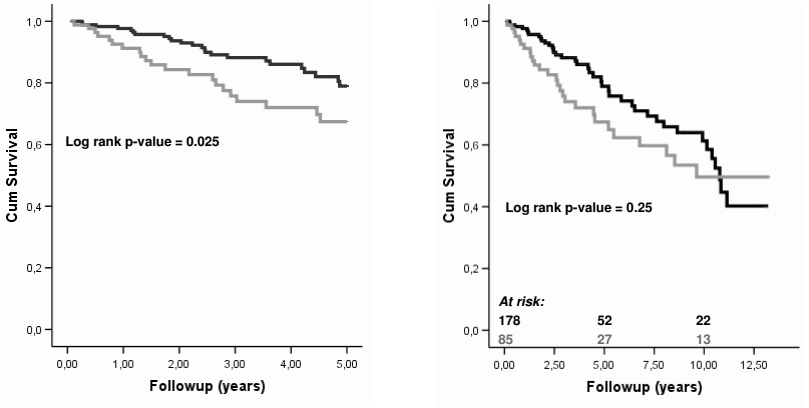
Figure 1. Survival curves of all cause mortality at 5 years and total follow-up of delta total walking distance, resting or exercise ankle brachial index.



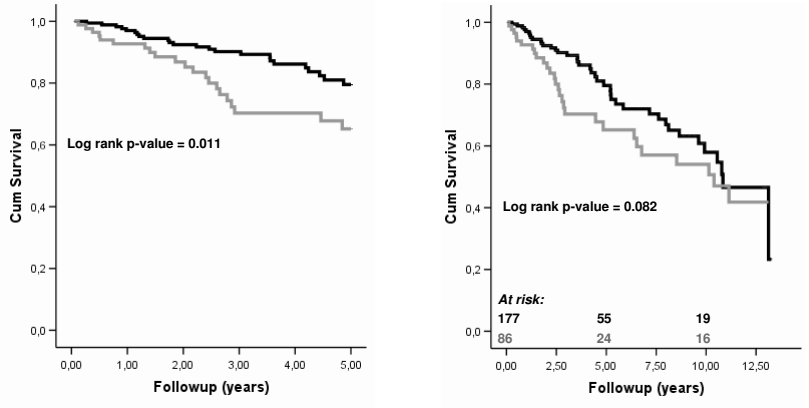
1a. Delta total walking distance

Stable or improved

Decline

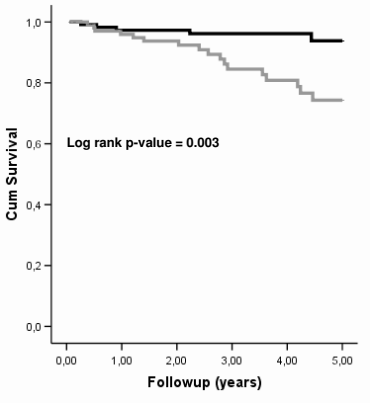


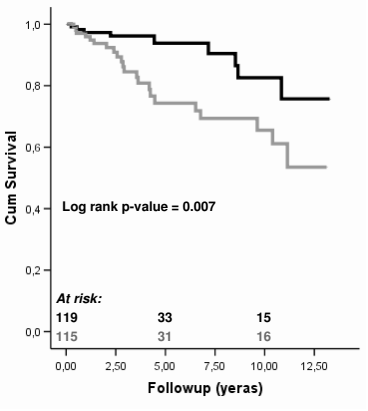
1b. Delta resting ankle brachial index



1c. Delta exercise ankle brachial index

Figure 2. Survival curves of cardiac death at 5 years and total follow-up of the delta total walking distance, resting or exercise ankle brachial index.

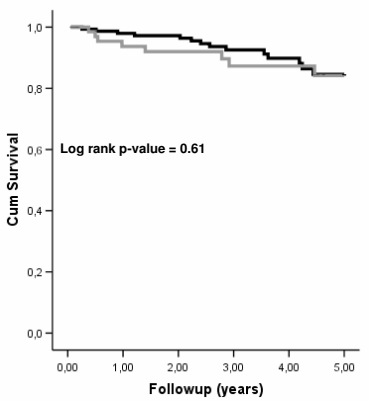


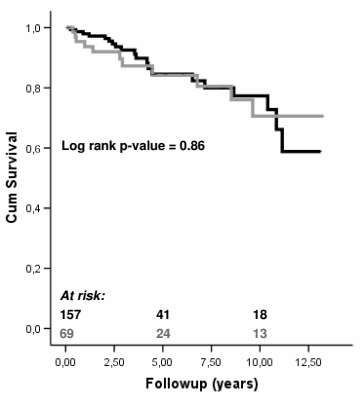


2a. Delta total walking distance

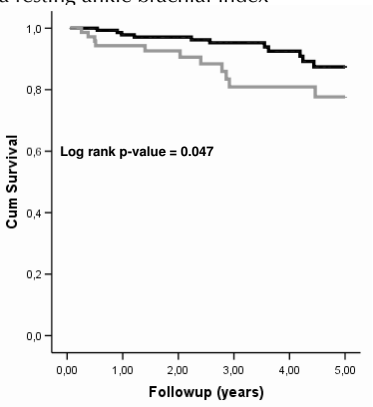
Stable or improved

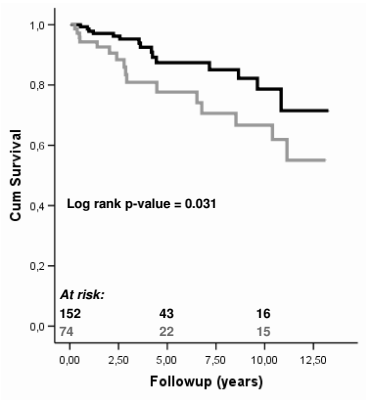
Decline





2b. Delta resting ankle brachial index





2c. Delta exercise ankle brachial index

because as far as we know, we were the first who explored this association. The underlying mechanism which may be responsible for our results, presented in this study, could unfortunately not be determined from our current data. However, one could imagine that the decline in walking performance reflects the progression of PAD. It is acknowledged that PAD is a manifestation of a systemic arthrosclerosis, which occur throughout the entire body not only in the lower limbs. The decline in walking distance probably reflects this progression of the systemic arteriosclerosis better then the ABI, which is only a measurement of diseases progression at the lower limbs. This was shown by Nicoloff et al [18]. They observed that patients with PAD experience symptoms of progression of lower-extremity, cerebrovascular and coronary disease, indicating that systemic arthrosclerosis indeed occur at various sites [18]. Unfortunately, there are no studies who investigated the relation between a decrease in walking distance and quantitative measurements of atherosclerosis. However, there are a few studies which showed that improvement in physical activity can improve carotid and coronary arthrosclerosis [19, 20]. Although, the pathophysiology behind the relationship between physical activity and arteriosclerosis is still unclear, researches has shown that the vascular endothelium plays an important role [19, 21-24]. Vascular endothelium is an imported regulator of the vascular homeostasis, regulating the vascular tone by producing vasodilator compounds, smooth muscle cell function, platelet aggregation and cell adhesion [19, 21, 24-26]. Vascular endothelium dysfunction occur early in patients with cardiovascular diseases, is likely responsible for the cardiovascular morbidity and mortality and can be influenced by physical activity [19, 21, 22, 24-26].

Besides our strength such as the long follow-up time, our study has it's limitations as well. The study is performed in a tertiary hospital, therefore it is unknown whether results are generalizable to the common population. However, other hospitals, which do not have a vascular laboratory or general practitioners sent their patients to the Erasmus MC particular for a treadmill exercise test. As a result, our study population not only includes patients from a tertiary hospital but also from local hospitals and general practitioners. Therefore we think that our study population is a representative population of a daily clinical vascular laboratory practice. Second, it would be ideal if time between the two tests was the same for all patients. Unfortunately, this was not the case. However, we made adjustments for the time between the two tests in the analyses to overcome this problem.

In conclusion, a decline in total walking distance at single-stage treadmill exercise tests is a strong independent prognostic predictor of all cause mortality and cardiac death at both on the short- and long-term. This functional evaluation adds prognostic data and should be repeatedly assessed during follow-up. Further studies are needed to reveal the underling mechanisms and effective treatments to improve the long-term outcome in these patients.

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Exercise test parameters

9

The value of treadmill exercise test parameters together in patients with known or suspected peripheral arterial disease

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ABSTRACT

Background: Exercise ankle brachial index (ABI) test parameters (exercise ABI, walking distance and blood pressure response) separately are associated with long-term outcome in patients with known or suspected for peripheral arterial disease (PAD). However, the clinical value of the combination of these parameters together are unknown.

Methods: 2165 patients performed a treadmill exercise test to diagnose or to evaluate their PAD. Resting ABI, exercise ABI, abnormal blood pressure response (hypotensive and hypertensive) and walking distance (impairment (< 150 meters) were measured. The study population was divided into patients with a resting ABI ≥ 0.90 and patients with PAD (resting ABI < 0.90).

Results: The mean follow-up period was 5 years (0.5-14 years). Long-term mortality rate and risks increases when more exercise parameters became abnormal. Patients with a normal resting ABI but with an abnormal exercise test were having a higher mortality risk (HR 1.90 (1.32 - 2.73)) and cardiac death (HR 3.24 (1.89 - 6.43)) than patients with a normal exercise test. The highest mortality risk and cardiac death was observed in PAD patients with a walking impairment together with an abnormal blood pressure response (HR 3.48 (2.22 - 5.46), HR 7.52 (3.69-15.33), respectively).

Conclusion: Exercise tests give multiple parameters, which together provide important prognostic information on long-term outcome in both patients with normal resting ABI and PAD.

INTRODUCTION

Peripheral arterial disease (PAD) is a manifestation of systemic arteriosclerosis and is affecting millions of people [1]. According to the guidelines, an ankle brachial index measured at rest (resting ABI) of less than 0.90 is defined as PAD and is related to a higher cardiovascular morbidity and mortality [2-4]. However, recent publications showed that resting ABI values between 0.90 - 1.10 are already associated with a higher mortality risk, impairment in physical performance and subclinical atherosclerosis of the coronary and carotid arterial beds [5-11]. However, a previous study observed that almost 30% of the patients with a resting ABI ≥ 0.90 showed to have an ABI < 0.90 after an exercise test. At these exercise tests, however, not only exercise ABI but other parameters, such as walking distance and blood pressure are measured as well. We previously demonstrated that a hypertensive or hypotensive blood pressure response (BPR) at a treadmill exercise test both were associated with a 2 fold increased risk of cardiovascular death [12, 13]. Also walking distance impairment was strongly associated with mortality, cardiac death and quality of life in both patients with ABI <0.90 and ≥ 0.90 [14-16]. However, it is not known if the combination of the different exercise parameters together adds additional prognostic information to the current known risk factors. Therefore, we performed a large observational study in our vascular laboratory to investigate the effects of the combination of treadmill exercise parameters together on long-term outcome in patients with suspected or already known PAD.

MATERIALS AND METHODS

Study Population

Our study population consisted of 2165 patients, who were referred by general practitioners or physicians to the vascular laboratory of the Erasmus Medical Centre, Rotterdam, the Netherlands, for a single-stage treadmill exercise test, between 1993 and 2006. Patients were referred by physicians to diagnose PAD, based on their presenting symptoms. Or patients, who already had a history of intermittent claudication or other symptoms of arterial insufficiency, were sent to evaluate their PAD. Excluded were patients who were unable to perform the treadmill exercise test.

Single-stage exercise test

Specialised trained personnel supervised the exercise tests, using a prescribed protocol. Patients were asked not to smoke before the test. The systolic blood pressure was measured with a blood pressure device (Maxi stable 3, presso stabl; Welch Allyn Inc, Skaneateles Falls, New York, USA) with 40% of the limb contour at both left and right arms in supine position after 15 minutes rest. In addition, the blood pressure at the anterior tibial and

posterial tibial arteries were measured at both sides, using a Doppler ultrasonic instrument with a 8-MHZ vascular probe (Imexdop CT+ vascular Doppler; Miami Medical, GlenAllen, Va). After these measurements all patients were asked to walk on a treadmill with a speed of 4 km/h for a maximum of 5 minutes. No inclining plane or graded inclines were used. During the walking test patients were ask to tell the personnel when they started to feel pain in the legs. Patients were encouraged to finish the whole test. Time and walking distance till the occurrence of leg pain and the total walking time and distance were recorded. Immediately after the exercise the systolic blood pressure at the arm, as well as at the anterior tibia or posterial tibial artery, depending which one was highest at rest, were measured in supine position. ABI at rest and after the exercise test were calculated by dividing the systolic blood pressure at the dorsalis pedis or posterial tibial arteries, depending which one was the highest, by the highest systolic blood pressure at the arm. For the resting ABI the interobserver and intraobserver agreement was 97% and 98%, and for the exercise ABI 96% and 97%, as described previously [17]. All variables were incorporated in a computerised hospital database. Patients with a resting ABI < 0.90 were defined as PAD.

Definition of treadmill exercise parameters

At the exercise test we measured three parameters namely; exercise ABI, abnormal blood pressure response (BPR) and total walking distance.

An abnormal BPR at the treadmill exercise test was defined as a hypertensive or a hypotensive BPR. As we described previously, we defined a hypertensive BPR as an increase in systolic blood pressure at the exercise test of ≥ 55mmHg (the 95th percentile), the difference between the highest measured exercise systolic blood pressure and the highest measured resting systolic blood pressure [12, 18]. Patients with an increase in systolic blood pressure of < 55mmHg were defined as having a normal BPR [12]. Subjects who experienced a decline in systolic blood pressure after the exercise compared to the resting systolic blood pressure were defined as having a hypotensive BPR [13]. For detailed description and discussion about the definitions of the hypertensive and hypotensive blood pressure response, we referred to the previous published articles [12, 13].

The exercise total walking distance was used as a continue variable and was categorised into quartiles for the whole population [14]. The lowest walking distance quartile, was defined as a severe walking impairment (less than 150 meters at the treadmill exercise test.) We previously observed that this severe walking impairment at the exercise test was significantly associated with a higher cardiovascular mortality in both patients with a resting ABI < 0.90 and ≥ 0.90 [14].

Covariate assessment

From the medical records, the following baseline characteristics were collected: age, gender, current smoking, diabetes mellitus, hypercholesterolemia, atrial fibrillation or sinus

tachycardia on 2-lead electrocardiography, hypertension, chronic obstructive pulmonary disease, renal dysfunction, history of congestive heart failure, history of myocardial infarction and history of coronary artery revascularisation. The following definitions were used for the different covariates. Diabetes mellitus was documented when patients presented with the diagnosis, made by the referred physician, required anti-diabetic medication, having a fasting glucose level ≥ 126mg/dl, a glucose level of ≥ 200mg/dl after a oral glucose tolerance test or plasma non-fasting glucose levels of ≥ 200mg/dl [19, 20]. Hypertension was recorded if a patient had a blood pressure higher > 140/90mmHg or treated with antihypertensive medication. Chronic obstructive pulmonary disease was classified as a history of chronic obstructive pulmonary disease or pulmonary medication use. Hypercholesterolemia was noted when patients presented with the diagnosis, made by the referred physician, received lipid-lowering medication or a plasma cholesterol level of 212mg/dl or more. Renal dysfunction was defined as having a serum creatinine level of ≥2.0 mg/dl or receiving dialyses.

Follow-up

The follow-up vital status, which was obtained by reviewing the civil registries, was completed for 99.4%. The survival status of six patients who had moved abroad could not be retrieved and the last available follow-up data were used. The cause of death was obtained from the Central Bureau of Statistics or from medical records. Of 62 patients (10%) no course of death could be traced. Additionally, to all survivors, a self-reporting questionnaire about cardiac events were sent, of whom 73% returned the questionnaire.

Statistical methods

Patients with a resting ABI > 1.30 (10 patients) were excluded from the analyses. The study population was divided into patients with a resting ABI ≥ 0.90 and patients with PAD (resting ABI < 0.90). To identify differences in baseline characteristics between patients with PAD and patients with normal resting ABI, student's t- tests for continuous variables and chi-square tests for categorical variables were used.

Multivariate Cox proportional hazard regression analyses were used to investigate the additional value of the combination of the treadmill exercise parameters (exercise ABI, walking distance and BPR) on long-term mortality risk in both patient with resting ABI ≥ 0.90 and patients with PAD. Included variables in the baseline model were age, gender, current smoking, diabetes mellitus, hypercholesterolemia, hypertension, atrial fibrillation or sinus tachycardia, chronic obstructive pulmonary disease, renal dysfunction, history of congestive heart failure, history of cardiac disease consisted of angina pectoris, myocardial infarction or coronary artery revascularisation and resting systolic blood pressure. The enter method was used, adding the different treadmill exercise parameters into the baseline model, to investigate the additional prognostic value on long-term mortality. However,

to confirm the proportional hazard assumption, first the proportionality of hazards were tested graphically based on visual inspection of log-log survival curves.
Next, based on the analyses above, the two groups were divided into a total of six patient groups. Then cox proportional hazard ratio's (HR) with 95% confidence interval (95% CI) were calculated to define the relationship between the different patient groups and long-term mortality, cardiac death and MACCE. MACCE consisted of cardiac or cerebrovascular death or major adverse cardiac events such as angina pectoris, non-fatal myocardial infarction, coronary artery bypass grafting or percutaneous coronary angioplasty. Additional adjustments were made for baseline medication use (statin, aspirin, beta-blockers, ACE-inhibitors). For all tests significance was defined as a p-value of ≤ 0.05. Analyses were performed in SPSS 15 for windows.

RESULTS

The mean follow-up period was 5 years (ranging from 0.5 years till 14 years). The mean age of the total population was 62 years (±12 sd) and 67% were men.
The log-log survival curves to test the proportionality of hazards did not show interactions with time. Table 1 shows the baseline characteristics of the two patient groups: patients with a resting ABI ≥ 0.90 and patients with PAD.
In patients with resting ABI ≥ 0.90 the multivariate Cox proportional hazard regression analyses revealed that both exercise ABI (p-value 0.02) and walking distance (p-value 0.03) added significant prognostic value, but abnormal BPR did not (table 2a).
In patient with PAD, the multivariate Cox proportional hazard regression analyses, demonstrated that both walking distance (p-value 0.0001) and abnormal BPR (p-value 0.004) added significant additional value on long-term mortality, but exercise ABI did not (table 2b). Comparable results were seen for cardiac death and MACCE.
Based on these results above the study population was split into 6 patient groups shown in table 3. The mortality rate and MACCE increases when more exercise tests became abnormal, p-trend 0.0001 (figure 1). After adjustment for potential clinical risk factors, patients with a resting ABI ≥ 0.90 but an abnormal exercise test (group 2 and 3) had a two to three fold higher risk of all cause mortality, cardiac death and MACCE compared with patients with a normal exercise test (group 1). PAD patients with one abnormal exercise test parameter had a two and a half fold increased risk of all cause mortality and a four fold increased risk of cardiac death and MACCE. The highest mortality risk was observed in PAD patients with both a walking distance impairment and an abnormal blood pressure response. The results did not change when all analyses were repeated with additional adjustments for baseline medication use (aspirin, statins, beta-blockers and ace-inhibitors).

Table 1. Baseline characteristics in patients with resting ABI ≥ *0.90* and patients with PAD.

Characteristics	*Resting ABI ≥ 0.90*	*PAD*	*p-value*
	n= 829	*n=1336*	
Age (years)	60 ± 13	64 ± 11	0.0001
Body mass index (kg/m^2)	27 ± 5	26 ± 8	0.2
Male (%)	508 (61)	943 (71)	0.0001
COPD (%)	105 (13)	174 (13)	0.8
Hypertension (%)	248 (30)	543 (41)	0.0001
Diabetes mellitus (%)	150 (18)	256 (19)	0.5
Current smoking (%)	236 (29)	461 (35)	0.03
Atrial fibrillation (%)	20 (3)	45 (4)	0.2
Hypercholesterolemia (%)	206 (25)	446 (26)	0.5
Renal failure (%)	61 (8)	80 (6)	0.3
History of cardiac disease (%)	266 (32)	457 (35)	0.4
History of heart failure (%)	44 (5)	86 (7)	0.3

Values are means with standard deviations or numbers with percentages.

DISCUSSION

In this study we showed for the first time that the combination of the different treadmill exercise parameters (exercise ABI, walking distance and BPR) together add prognostic information to the current known risk factors on long-term outcome in both patients with a resting ABI ≥ 0.90 and PAD. The more the exercise parameters became abnormal the worse the long-term outcome became.

PAD is a manifestation of systemic arteriosclerosis, affecting millions of people [1]. The ABI is used to assess peripheral arterial stenosis [21]. According to the guidelines, a resting ABI < 0.90 is defined as PAD, which is related to a higher cardiovascular morbidity and mortality [2-4, 17, 22]. In clinical practice, mostly the resting ABI is used. Exercise ABI could give important information on long-term outcome. However, exercise test may also provide other clinical data, such as blood pressure and walking distance, which may also be used to identify patients with increased mortality risks [12-14]. We previously showed, for example, that a hypertensive BPR, a hypotensive BPR and an impairment in walking distance at a treadmill exercise test, were all important and independent risk factors of long-term outcome in patients with known or suspected for PAD [12-14]. However, the prognostic value of the combination of the different exercise test parameters together has not been investigated before. In this study we demonstrated that resting ABI, exercise ABI, walking distance and BPR all add additional prognostic information to the current known risk factors on long-term outcome. The more the exercise test results were abnormal the

Table 2. Chi square and hazard ratio's with 95% confidence intervals after multivariate cox proportional hazard regression analyses on long-term mortality in patients with resting ABI ≥ *0.90* and PAD.

2a.

Resting ABI ≥ 0.90	Model II = Model I **+ resting ABI**	Model III = Model II **+ exercise ABI**	Model IV = Model III **+ walking distance**	Model V = Model IV **+ abnormal BPR**
X^2	**8.861**	**5.646**	**4.562**	1.288
p-value	**0.003**	**0.02**	**0.03**	0.26
HR (95% CI):				
Resting ABI	**0.97 (0.94-0.99)**	0.98 (0.96 - 1.01)	0.98 (0.96 - 1.01)	0.98 (0.96 - 1.01)
Exercise ABI	**-**	**0.99 (0.98 -0.99)**	**0.99 (0.98 - 0.99)**	**0.99 (0.98 - 0.99)**
Walking distance	**-**	**-**	**0.99 (0.99 - 0.99)**	**0.99 (0.99 - 1.00)**
Abnormal BPR	**-**	**-**	**-**	1.34 (0.81 - 2.21)

2b.

PAD	Model II = Model I **+ resting ABI**	Model III = Model II **+ exercise ABI**	Model IV = Model III **+ walking distance**	Model V = Model IV **+ abnormal BPR**
X^2	**7.847**	0.117	**13.945**	**8.445**
p-value	**0.005**	0.73	**0.0001**	**0.004**
HR (95% CI):				
Resting ABI	**0.99 (0.98-0.99)**	**0.99 (0.98-0.99)**	0.99 (0.98 - 1.00)	0.99 (.99 - 1.00)
Exercise ABI	**-**	1.00 (0.99-1.01)	1.00 (0.99 - 1.01)	1.00 (0.99 - 1.01)
Walking distance	**-**	**-**	**0.99 (0.99 - 0.99)**	**0.99 (0.99 - 0.99)**
Abnormal BPR	**-**	**-**	**-**	**1.46 (1.13 - 1.88)**

Model I = baseline characteristics = age, gender, current smoking at baseline, atrial fibrillation or sinus tachycardia, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, renal failure and resting systolic blood pressure

worse the long-term outcome became, with the highest mortality in PAD patients with an abnormal blood pressure response and a walking impairment.

Because we are the first who investigated these associations together, our results could not be compared to other researches. Also no other researches were done to reveal the under laying mechanisms. However, it could be hypothesised that the exercise test parameters together probably reflects systemic atherosclerosis better than one parameter individually. Atherosclerosis is a systemic disease, which occur throughout the entire body with different symptoms at different sites [23]. For example, hypertensive BPR is a result of endothelial dysfunction, sympathetic nerve system dysfunction or activation of mechanosensitive and metabolsensitive reflexes caused by generalised atherosclerosis [12, 24-28]. A hypotensive BPR at exercise is explained by severe atherosclerosis of the coronary arteries resulting in heart failure or left ventricular dysfunction during exercise [29-32]. Probably, the different parameters together give more information of the extensiveness of the disease and there-

Table 3. Description of the six patient groups depending of the exercise test results.

Groups		NA
1. (reference)	**Resting ABI ≥ 0.90: Exercise ABI ≥ 0.90, AND no walking impairment**	**438**
2.	**Resting ABI ≥ 0.90: Exercise ABI < 0.90 OR walking impairment**	**335**
3.	**Resting ABI ≥ 0.90: Exercise ABI < 0.90 AND walking impairment**	**56**
4.	**PAD, No walking impairment, AND normal BPR**	**778**
5.	**PAD, walking impairment OR abnormal BPR**	**501**
6.	**PAD, walking impairment AND abnormal BPR**	**57**

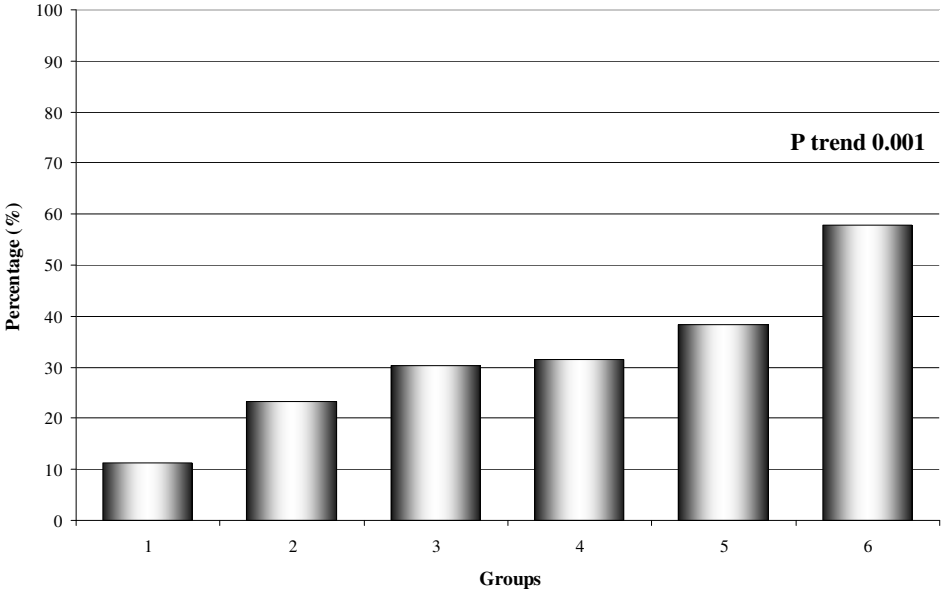
fore gives important additional information on long-term outcome. As a result, good risk identification thus needs not only resting ABI measurements, but also exercise testing. However, further research is needed to investigate if these mortality risks can be changed by adding additional treatments or giving different treatment regimes for each patient group.

Besides our strength such as the large study population and long follow-up, our study has it's limitations as well. The study is performed in a tertiary hospital, therefore it is unknown whether results are generalizable in the common population. However, other hospitals, which do not have a vascular laboratory, or general practitioners sent their patients to the Erasmus MC particular for a treadmill exercise test. Therefore, our data is a representative mixture of a daily clinical practice in an average vascular laboratory.

In conclusion, combining different treadmill exercise test parameters together, add additional prognostic information to the current known risk factors on long-term outcome in both patients with a resting ABI ≥ 0.90 and PAD. Therefore, exercise tests are important to identify patients with increased mortality risks. However, further research is needed to investigate which and when treatment is needed to improve long-term outcome in these patients.

Figure 1. All cause long-term mortality rates and MACCE of the six patient groups.

1a. All cause mortality



1b. MACCE

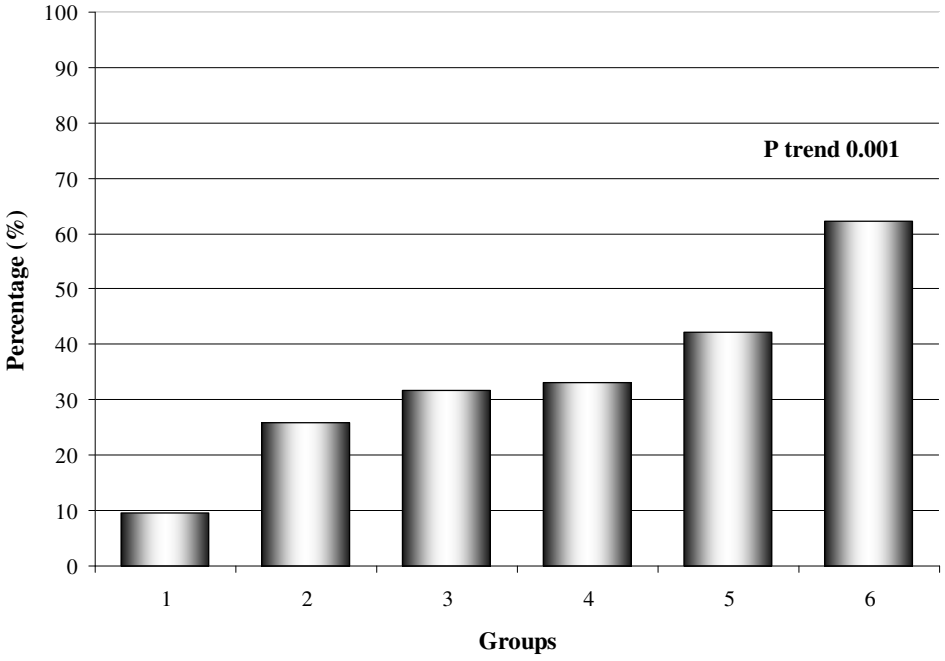


Table 4. Hazard ratio's and 95% confidence intervals on long-term mortality in the six patient groups.

Groups:	*Model I* *HR (95% CI)*			*Model II* *HR (95% CI)*		
All cause mortality						
1	Reference			Reference		
2	**1.94**	**(1.36**	**2.78)**	**1.98**	**(1.37**	**2.85)**
3	**2.07**	**(1.19**	**3.59)**	**2.02**	**(1.15**	**3.54)**
4	**1.83**	**(1.35**	**2.49)**	**1.83**	**(1.33**	**2.51)**
5	**2.47**	**(1.80**	**3.39)**	**2.45**	**(1.77**	**3.39)**
6	**3.36**	**(2.16**	**5.22)**	**3.54**	**(2.25**	**5.55)**
Cardiac death						
1	Reference			Reference		
2	**3.55**	**(1.93**	**6.54)**	**3.59**	**(1.95**	**6.62)**
3	**3.38**	**(1.30**	**8.80)**	**3.27**	**(1.25**	**8.57)**
4	**3.13**	**(1.79**	**5.47)**	**3.22**	**(1.84**	**5.65)**
5	**4.40**	**(2.50**	**7.76)**	**4.31**	**(2.43**	**7.63)**
6	**7.38**	**(3.63**	**14.99)**	**7.75**	**(3.79**	**15.83)**
MACCE						
1	Reference			Reference		
2	**2.70**	**(1.74**	**4.21)**	**2.55**	**(1.63**	**3.98)**
3	**4.19**	**(2.14**	**8.19)**	**3.30**	**(1.67**	**6.53)**
4	**2.60**	**(1.76**	**3.84)**	**2.48**	**(1.67**	**3.66)**
5	**3.99**	**(2.68**	**5.96)**	**3.54**	**(2.36**	**5.29)**
6	**5.97**	**(3.46**	**10.32)**	**5.24**	**(3.02**	**9.08)**

Model I: age and gender

Model II: model I and current smoking at baseline, atrial fibrillation or sinus tachycardia, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, renal failure and resting systolic blood pressure

Bold characters are significant values with p-value ≤ 0.05

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The Association between Peripheral Arterial Disease, Treadmill Exercise Test Parameters and Long-Term Outcome

10

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ABSTRACT

Peripheral arterial disease (PAD), a manifestation of systemic artheriosclerosis, is affecting millions of people with prevalences between 4 to 29%, and is expected to rise in the following decades [1, 2]. According to the guidelines, a resting ankle brachial index (ABI) < 0.90 is defined as PAD, which is related to a higher cardiovascular morbidity and mortality [3, 4]. Surprisingly, in contrast to patients with coronary arterial disease, the value of the exercise test in patients with PAD is still unclear and hardly investigated. Nevertheless, the exercise test may provide a large amount of important clinical data to identify patients with increased cardiovascular risks. Recent publications have also shown that resting ABI between 0.90–1.10, thus classified as 'normal' according to the guidelines, was associated with a higher mortality [5-7]. In today's clinical practice, the ABI measured at rest is still the most used method to diagnose PAD. However, more than 30% of the patients with resting ABI ≥ 0.90 demonstrated after a treadmill exercise test an ABI <0.90 and were associated with a higher mortality rate [8]. These patients would have been missed according to the current definitions. Not only exercise ABI, but also other factors which may have an important role in the prognosis of PAD can be identified with exercise tests. For example, a hypertensive blood pressure response and a hypotensive blood pressure response at a treadmill exercise test, are associated with an almost two-fold increased risk of cardiovascular death [9, 10]. Also, walking distance impairment was strongly associated with mortality, cardiac death and quality of life [11, 12]. Combining treadmill variables, exercise ABI, walking distance and blood pressure response, with the current known risk factors, provides important additional prognostic information of cardiovascular morbidity and mortality. Furthermore, not only a decline in ABI, but also a decline in walking distance turned out to be a strong prognostic factor of long-term mortality as well [13]. This indicates that exercise tests could be used not only for risk stratification but also for identifying progressive disease.

Exercise tests might also be used for early risk factor modification. For instance, early treatment of cardiovascular risk factors such as life style changes, exercise training and optimal medical treatment with statins and beta-blockers, for example, have shown to be effective in patients with PAD [2, 4, 14, 15]. However, it is unknown if, when and how patients, especially with mild and borderline impaired ABI values must be treated.

In conclusion, treadmill exercise test parameters are important to identify patients with increased mortality risks, which would otherwise remain unrecognised and untreated, and to identify patients with progressive PAD. However, further research is needed to investigate which and when treatment is needed to lower cardiovascular risks in these patients.

INTRODUCTION

Peripheral arterial disease

Peripheral arterial disease (PAD) is a manifestation of systemic arteriosclerosis [1, 4, 16-19]. Study results indicate that the disease is not only limited at the lower limbs, but that it is a systemic disease affecting different sites of the human body [19-21]. It is a common disease affecting millions of people. Depending on the age of the invested population, in the United States of America prevalence between 4 to 29% has been reported [1, 2]. Patients with PAD are of an increased risk of cardiovascular events and mortality [3, 4, 22]. Some investigations observed that patients with PAD had a higher 1-year cardiovascular event rate than patients with coronary arterial disease [19, 23]. In addition to the higher risk of cardiovascular events and mortality, patients with PAD also experience significant limitations in their physical functioning and an impairment in their quality of life [12, 24-35]. It is alarming that the prevalence is expected to rise in the following decades due to the aging of the western population and the increase of risk factors such as diabetes mellitus, obesity and lack of exercise [1, 2, 19].

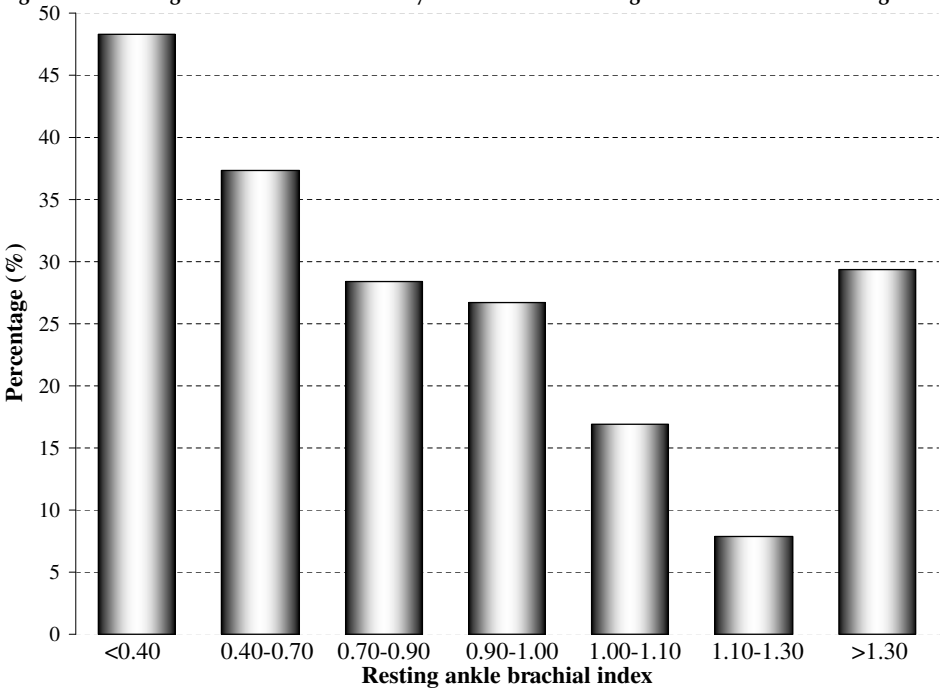
Therefore, it is important to diagnose patients with PAD early and to provide them optimal treatment as soon as possible in attempting to lower the complication rates and improve morbidity and mortality. However, symptoms of PAD are variable [19, 36, 37].The classical symptoms are intermittent claudication consisted of calf pain provoked by walking and declining at rest [36]. On the other hand, earlier investigations have demonstrated a large range of the clinical manifestations in PAD patients ranging from no pain at all till pain at rest [36, 38-42]. A major problem is that from 20% up to 50% of the patients are asymptomatic, but having already an increased risk of morbidity and mortality [4, 5, 16, 17, 19, 37, 41, 43]. With exercise tests these patients may be identified and treated accordingly. In contrast to the value of the exercise test in cardiac patients, the value of exercise tests in patients with PAD and with suspected PAD in particular is still unclear and hardly investigated. These exercise tests might play an important role in identifying patients with PAD early who would otherwise remain unnoticed. It could also provide a large amount of important clinical data on other important risk factors associated with cardiovascular morbidity and mortality. In addition, the exercise test could be an important tool to assess the progression of the disease and to evaluate treatment effects.

Resting ankle brachial index

According to the guidelines, the ankle brachial index (ABI) at rest is used to diagnose PAD [44]. It is calculated by dividing the systolic blood pressure at the dorsalis pedis or posterial tibial arteries, measured using a Doppler ultrasonic instrument, by the highest systolic blood pressure at the arm [4, 17, 18, 45]. Values of less than 0.90 are associated with vessel stenosis of more than 50% and is defined as PAD [4, 18, 46]. Several studies have found

that ABI of < 0.90 is associated with an increased risk of cardiovascular diseases and mortality and can be used for prognostic risk stratifications (Figure 1) [1, 22, 47].
Some patients have an ABI of more than 1.30. In these patients it is shown that they also have an increased risk of cardiovascular mortality when compared to patients with a

Figure 1. Percentage of all causes of mortality in the different resting ankle brachial index categories.



normal ABI (Figure 1) [4, 48, 49]. An ABI of more than 1.30 is more often observed in patients with diabetes mellitus and is thought to be due to serious calcification of vessels [4, 49, 50]. This results in high vessel wall rigidity and therefore abnormal highly measured systolic blood pressures in the legs, resulting in a high ABI [4, 49, 50].
Normally, the ankle systolic blood pressure is higher than the systolic blood pressure at the arm [51]. Therefore, ABI of less than 1.10, instead of 0.90, should be considered as abnormal [6, 7, 43]. Recent publications indeed showed that resting ABI between 0.90–1.10 was already associated with sub-clinical atherosclerosis of the coronary and carotid arterial beds, higher mortality rate and impairment in physical performance compared to patients with ABI between 1.10–1.30 (Figure 1) [1, 5-7, 20, 43, 52, 53]. However, using the current guidelines, these patients will not be considered as having PAD and will remain untreated.
Although in clinical practice resting ABI is used, two studies have shown that more than 35% of the patients with a normal resting ABI (ABI ≥ 0.90) fell below the 0.90 after a

treadmill exercise test [8, in press]. These patients would not be identified if the exercise test were not performed.

TREADMILL EXERCISE TEST

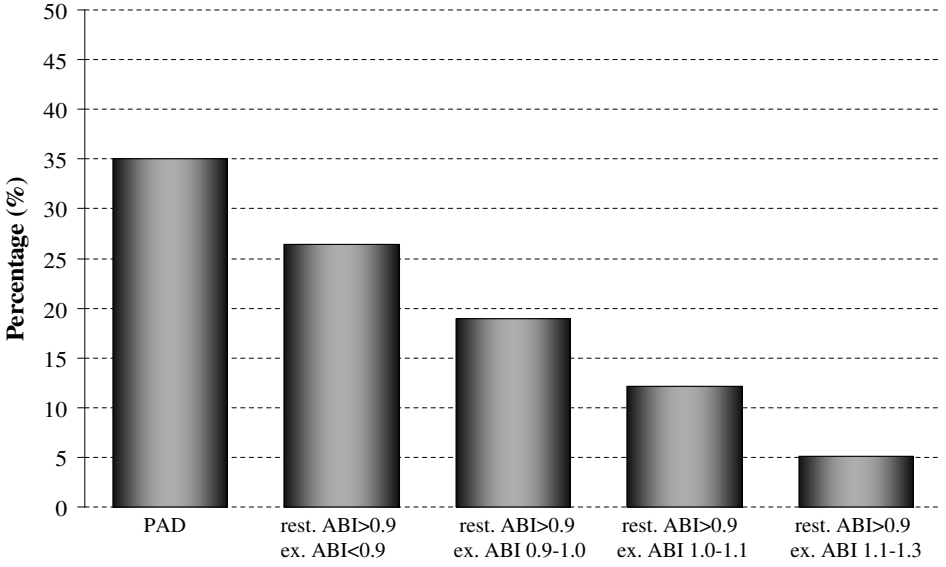
A treadmill exercise test is most often used, although there is not yet one international prescribed exercise protocol for patients with known or suspected PAD. The exercise test is mostly supervised by specially trained personnel of a vascular laboratory. First the systolic blood pressure will be measured at rest and the resting ankle arm index will be defined. After these measurements, the patients will be asked to walk on a treadmill with a speed ranging from 3.2km/h to 4 km/h for a maximum of 5 minutes. No graded inclines or slight increase of 2% per two minutes are used [16, 54]. During the walking test, patients will be asked to tell the personnel when they started to feel pain in their legs. Patients will be encouraged to finish the whole test, but the test will stop when the patient is unable to walk further. Time and walking distance till the occurrence of leg pain and the total walking time and distance are recorded. Immediately after the exercise the systolic blood pressure at the arm, as well as at the dorsalis pedis or posterial tibial artery will be measured and the ABI is calculated.

EXERCISE TEST PARAMETERS

Exercise ankle brachial index

As addressed above, according to the guidelines, a resting ABI < 0.90 is defined as PAD [1, 3, 4, 22, 47]. In clinical practice the resting ABI is most often used, especially in the primary care practise [8, 18]. Stein et al. showed that almost 30% of the patients, referred to the vascular laboratory, who had a normal resting ABI, were shown to have an exercise ABI < 0.90 [8]. Therefore, they advised that patients with a normal resting ABI, but with exertional limb symptoms, should undergo exercise testing [8]. Comparable results were observed by de Liefde et al. [in press]. They observed that more than 35% of the patients with normal resting ABI demonstrated an ABI <0.90 after a treadmill exercise test. Additionally, they investigated the additional prognostic value of the exercise ABI itself. They observed that exercise ABI added additional prognostic value on long-term mortality in patients with normal resting ABI (ABI > 0.90), but not in patients with PAD (resting ABI < 0.90). When patients with normal resting ABI were divided into four groups: exercise ABI < 0.90, exercise ABI between 0.90–1.00, 1.00–1.10 and 1.10–1.30 (reference group)—they observed that patients with an abnormal exercise ABI were of increased risk of long-term mortality (Figure 2) [in press]. The mortality risk significantly increased when the exercise ABI

Figure 2. Percentage of all causes of mortality in patients with PAD and four exercise ankle brachial index categories.



became worse (Figure 2). When using only the resting ABI, patients with impaired exercise ABI who have an increased mortality risk, will fail to be noticed. Using exercise tests to discover patients with subclinical PAD, early treatment could be started, although it is unknown when and how these patients should be treated and if they will benefit from it (see below). However, the authors also advocate that at least all patients, referred to a vascular laboratory, with a resting ABI ≥ 0.90 needs to undergo exercise testing.

Walking distance

An other variable recorded at a treadmill exercise test is the walking distance. In contrast to the clinical value of the ABI, the clinical value of walking disability is unclear. It has been shown previously in other populations such as in well-functioning community-based older adults or patients with impaired left ventricular function or congestive heart failure that a decreased performance at a walk test was a strong independent predictor of morbidity and mortality [55,56]. Recently, McDermott et al. showed that a severe impairment in walking distance at a 6-minute walking test in patients with PAD was significantly associated with all cause mortality and cardiovascular death [11]. However, they did not observed this relationship in patients with no PAD (resting ABI≥0.90). In contrast, a recent publication observed in both patient with PAD and patients with resting ABI ≥ 0.90 that the exercise walking distance was associated with an adverse long-term outcome, independent of other cardiovascular risk factors or ABI (Table 1) [54].

Table 1. Hazard ratios and 95% confidence intervals on all causes of mortality of walking impairment quartiles in patients with resting ABI ≥ 0.90 and patients with PAD

All cause mortality Total walking distance	HR (95% CI)		
Patients with ABI ≥ 0.90			
I no impairment	ref		
II mild impairment	1.70	(0.73	3.98)
III moderate impairment	1.57	(0.70	3.54)
IV severe impairment	**2.60**	**(1.16**	**5.78)**
Patients with PAD (ABI < 0.90)			
I no impairment	ref		
II mild impairment	*1.26*	*(0.95*	*1.67)*
III moderate impairment	**1.52**	**(1.13**	**2.05)**
IV severe impairment	**1.69**	**(1.21**	**2.27)**

Adjusted for: age, gender, current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, renal failure, resting systolic blood pressure and exercise ankle brachial index
Bold characters are significant values with p-value ≤ 0.05

Besides the relationship between walking distance, mortality risk and cardiac death associations between walking distance and quality of life are observed as well (Figure 3) [11, 12]. Although several studies have shown that patients with PAD have a lower quality of life compared to non-PAD control groups, most studies did not observed any association between the ABI and quality of life scores [12, 27-35]. However, in those few studies who investigated the association between walking distance and quality of life, a significant relation was found between total walking distance and physical health status, with evident dose-response relationships in patients with known or suspected PAD (Figure 3)[12, 30, 33, in press]. As a result, walking distance is not only a strong predictor of cardiovascular events and mortality, but for health status as well.

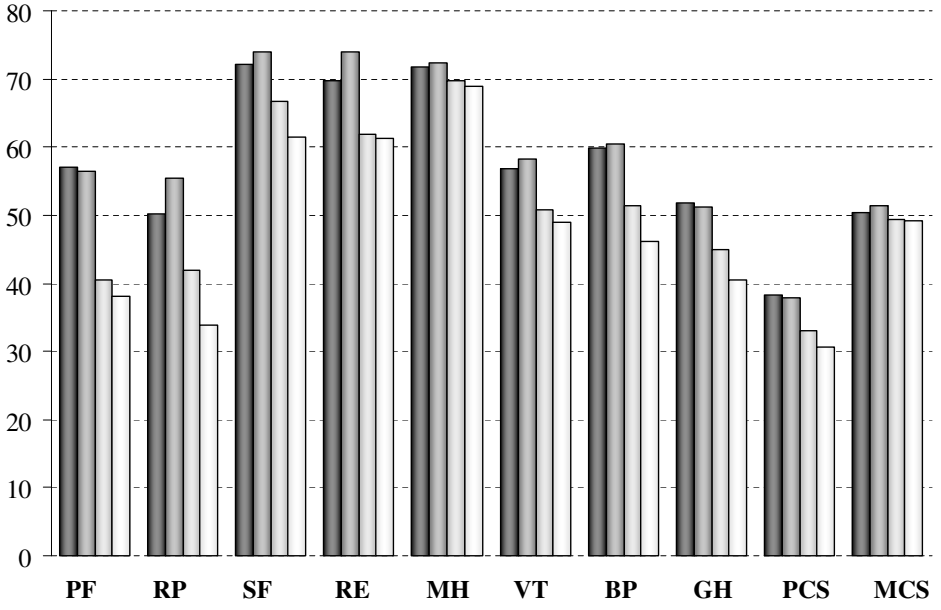
Blood pressure response

Blood pressure itself, which is always measured at least two times during a treadmill exercise test to calculate the resting and exercise ABI, also contains important information.

Hypertensive blood pressure response

A normal blood pressure response during dynamic exercise is a rise in the systolic blood pressure with no change or a slightly decrease in the diastolic blood pressure and widening of the pulse pressure [57]. A number of patients develop a hypertensive blood pressure response during an exercise test. Few studies have previously investigated the effects of a hypertensive blood pressure response at an exercise test in a healthy population [58-61]. A hypertensive blood pressure response was defined as a peak exercise systolic blood pressure of ≥ 200 mmHg or ≥ 210 in men and ≥ 190 mmHg in women in a healthy population, according to the Framingham criteria. It is observed that an hypertensive blood pressure

Figure 3. Mean scores on the eight sub-domains and two component scores of the SF-36 of walking impairment quartiles in patients with known or suspected peripheral arterial disease.



Physical functioning (PF). role limitation due to physical health problems (RP). social functioning (SF). role limitations due to emotional problems (RE). mental health (MH). vitality (VT). bodily pain (BP). general health (GH). physical health component score (PCS) and metal health component score (MCS).

response was associated with an increased risk of future hypertension and a higher risk of cardiovascular diseases and mortality [58-61]. Only one study investigated the effect of a hypertensive blood pressure response on cardiovascular events and mortality in patients with known or suspected PAD [9]. In this population, which contained patients with already established hypertension, the hypertensive blood pressure response was defined as an increase of systolic blood pressure at the exercise test of ≥ 55mmHg (95th percentile) compared to the resting systolic blood pressure. They observed that a hypertensive blood pressure response after a single-stage treadmill exercise tests in patients with known or suspected PAD was associated with a higher all cause long-term mortality, cardiovascular events and death (Table 2) [9].

There are a few possible mechanisms to explain the observed relationship between hypertensive blood pressure response and the observed higher mortality and cardiovascular event rate. During exercise the proportion of the cardiac output received by the skeletal muscles in general may increase from 20% to 80% [62-64]. It is found that patients with a hypertensive blood pressure response failed to show a decline in peripheral resistance [65].

Table 2. Hazard ratios and 95% confidence intervals on all cause mortality in patients with hypertensive blood pressure response and hypotensive blood pressure response on a single stage treadmill exercise test.

		HR (95% CI)
Hypertensive blood pressure response		
All cause mortality	**1.42**	**(1.12 - 1.80)**
Major adverse cerebrovascular and cardiac events	**1.47**	**(1.09 - 1.97)**
Hypotensive blood pressure response		
All cause mortality	**1.74**	**(1.10 - 2.73)**
Major adverse cerebrovascular and cardiac events	**1.85**	**(1.14 - 3.00)**

Adjusted for: age, gender, current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, renal failure, systolic blood pressure at rest and ankle brachial index at rest. **Bold** characters are significant values with p-value ≤ 0.05

This suggests a failure in the capacity of exercise induced vasodilation, probably due to a poor arterial compliance. This is probably the result of generalised atherosclerosis, dysfunction of the sympatic nerve system, which increases the vascular tone, or vascular endothelial dysfunction, which is an imported regulator of the vascular tone by producing vasodilator compounds such as NO [63, 64, 66, 67]. Besides, it is possible that due to generalised atherosclerosis, patients suffer from muscular ischemia during the exercise test, which results in an activation of the mechanosensitive or metabolsensitive reflex, a powerful pressure rising reflex in response to ischemia, resulting in an excessive rise of the blood pressure [62, 68].

Hypotensive blood pressure response

Instead of a rise in systolic blood pressure, some patients demonstrate a decline in systolic blood pressure during an exercise test. In cardiac patients, a hypotensive blood pressure response at an exercise test is thought to be a sign of severe coronary artery disease and is associated with a higher cardiovascular death [69-72]. Comparable results were observed for patients with PAD [10]. Patients with known or suspected PAD with a decline in systolic blood pressure after a treadmill exercise test had an increased risk of all cause mortality and cardiovascular events (table 2) [10].

A few mechanisms may explain this hypotensive blood pressure response at exercise. Healthy subjects may show a hypotensive blood pressure response but only after prolonged and vigorous exercise [57, 73]. Hypovolemia and valvular disease can also produce a hypotensive blood pressure response at exercise, as well as medication use, such as beta-blockers. However, the most commonly and invested explanation for the hypotensive blood pressure response after exercise, is heart failure or left ventricular dysfunction resulting from severe coronary artery disease, which was shown by several researches [57, 69, 70, 74, 75].

Clinicians should be aware that the presentation of an abnormal blood pressure response at a treadmill exercise test might be an important risk factor for all cause mortality and cardiovascular events in patients with PAD or who are suspected for PAD, which should not be denied.

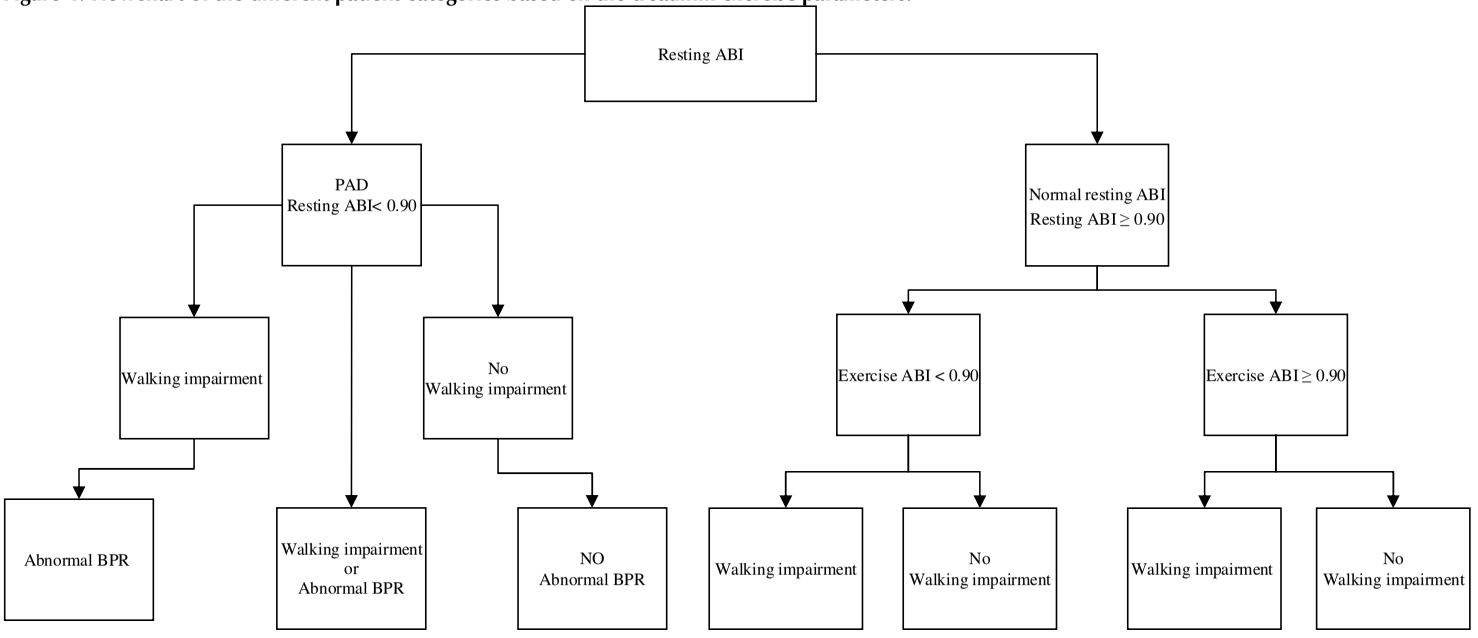
EXERCISE PARAMETERS COMBINED

Exercise ABI, walking distance and blood pressure response are risk factor measurements resulting of treadmill exercise tests. An important question arises: does these exercise parameters add additional value above the already known risk factors and measurements at rest to predict long-term outcome.
In patients with a normal resting ABI (ABI ≥ 0.90) it was observed that both exercise ABI and walking impairment added prognostic value to the already known clinical risk factors such as age, gender, smoking, diabetes mellitus, previous cardiac diseases, hypertension, renal failure. In patients with PAD walking impairment and blood pressure response added important prognostic value in the association with long-term outcome, but the exercise ABI did not. After deviding patients into seven groups, depending the results described above, it was shown that the mortality increases when more exercise parameters became abnormal (Figure 4 and 5). The worst prognosis was observed in patients with PAD (resting ABI < 0.90), walking impairment (distance < 150 meters) and an abnormal blood pressure response (Figure 5) [in press].

REPEATED MEASUREMENTS

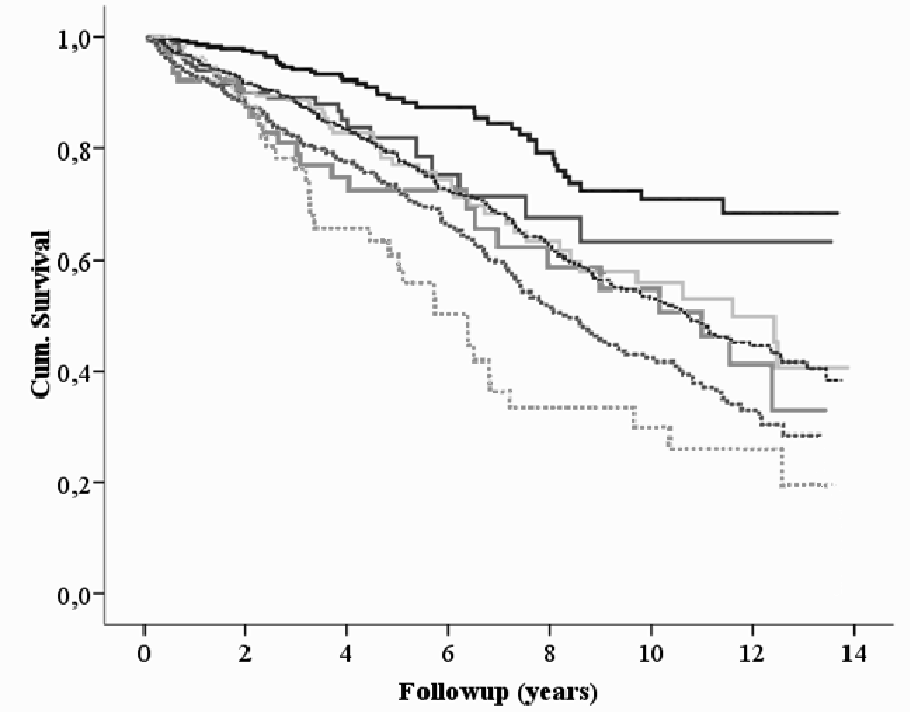
Besides baseline measurements, exercise test could also be used to evaluate the progression of the disease. In patients with coronary arteriosclerosis, Azen et al has shown that progression of the coronary arteriosclerosis was related with a higher rate of coronary events [76]. In patients with PAD, Criqiu et al. observed that a decline of more than 0.15 points between the baseline resting ABI and a second resting ABI measurement, was significant and independent associated with a higher all-cause mortality and cardiovascular mortality at three years follow-up [13]. An other study observed that a decrease in walking distance between two tests, without surgery between the measurements, was strongly related with a higher long-term mortality rate independent of clinical risk factors and ABI (table 3) [77]. The decline in walking distance probably reflects the progression of the systemic arteriosclerosis although unfortunately there are no studies yet who has approved this assumption with quantitative measurements. However, these results indicate that exercise tests may not only be used to identify patients at risk, but could also be used as a tool to monitor the progression of the disease.

Figure 4. Flowchart of the different patient categories based on the treadmill exercise parameters.



ABI = ankle brachial index; PAD = peripheral arterial disease; BPR = blood pressure response
Walking impairment = total walking distance < 150 meters
Abnormal BPR = hypertensive or hypotensive blood pressure response

Figure 5. Survival curves of the seven groups based on the different exercise test parameters.



Groups:

1. **- Normal ABI >0.90 + exercise ABI >0.90 + normal walking distance**
2. **- Normal resting ABI + exercise ABI >0.90 + impaired walking distance**
3. **- Normal resting ABI + exercise ABI <0.90 + normal walking distance**
4. **- Normal resting ABI + exercise ABI <0.90 + impaired walking distance**
5. **- - PAD + normal walking distance + normal BPR**
6. **- - PAD + impaired walking distance or abnormal BPR**
7. **- - PAD + impaired walking distance + abnormal BPR**

Table 3. Hazard ratios and 95% confidence intervals on all cause mortality and cardiac death in patients with a decline in walking distance on a treadmill exercise test to evaluate or diagnose peripheral arterial disease

Walking distance	HR (95% CI)
All cause mortality	
Stable or improved (reference)	1
Declined walking distance	**2.15 (1.21-3.70)**
Cardiac death	
Stable or improved (reference)	**1**
Declined walking distance	**3.14 (1.27-7.80)**

Adjusted for: age, gender, current smoking at baseline, hypertension, chronic obstructive pulmonary disease, hypercholesterolemia, diabetes mellitus, history of congestive heart failure, previous cardiovascular diseases, renal failure, systolic blood pressure at rest and ankle brachial index at rest.
Bold characters are significant values with p-value ≤ 0.05

TREATMENT

Medical treatment in patients with PAD is extensively investigated, although until now when treatment must start and which regime is optimal is still unclear.

Risk factor modification and medical treatment

All patients with suspected PAD need to undergo risk factor modification. Stop smoking, reduce weight, tight control of diabetes mellitus, dietary restrictions to reduce weight, control hypercholesterolemia and hypertension [4, 16-19, 45].

Stop smoking reduces the risk of myocardial infarction, cardiovascular death and slows the progression of critical limb ischemia although it is unknown if stop smoking also reduces the symptoms of PAD [4, 17, 18, 45, 78-80].

Tight control of diabetes reduces the incidence of cardiovascular events, although it is still unclear whether is reduces cardiovascular events in PAD and if it will stop the progression of the disease [4, 17, 18, 45, 81, 82].

Hypercholesterolemia plays an important role in systemic arteriosclerosis. The goal in all patients with symptomatic and asymptomatic PAD is to achieve a low-density lipoprotein (LDL) cholesterol level of < 2.59 mmol/L (<100mg/dl) [4, 16-18, 46, 83-87]. In symptomatic patients with a history of cardiovascular events levels of < 1.81 mmol/L are aimed (<70mg/dl) [4, 16-18, 46, 83-87]. The cornerstone to achieve these goals is not only by dietary modifications but also using statins [4, 16-18, 46, 83-87]. A subgroup analysis in PAD patients of the Heart Protection Study collaborative group showed that simvastatin reduced major cardiac events [14]. Also improvement in ABI, walking performance and claudication symptoms has been reported [16, 83, 86, 87]. The protective effect of statin use on mortality may not only be due to the lipid-lowering effect, but also through an inhibitory effect of the inflammatory process observed in atherosclerosis, increase the bioavailability of NO, antioxidant properties and produce in plaque stabilisation [4, 88].

Hypertension, which is a risk factor for future myocardial infarction, stroke and heart failure, should be controlled with target ranges of <140/90mmHg. In patients with diabetes mellitus the target ranges are even tighter below 130/80 [17, 18]. The HOPE study showed that angiotensin converting enzyme (ACE) inhibitors (ramipril) reduce the risk of myocardial infarction, stroke and vascular death [89]. Therefore, ACE inhibitors are recommended in patient with PAD [17, 18].

Although ones beta-blockers were thought to be a contraindication in patients with PAD due to the risk of impairment of the peripheral circulation, they have shown to have cardiovascular protection, probably due to prevention of plaque disruption accomplished by lowering heart rate, blood pressure and anti-inflammatory properties [18, 90-92].

Besides statins, ace-inhibitors and beta-blockers, antiplatelet medication is an other important drug which reduces the risk of cardiovascular complications in PAD [4, 17, 18, 63, 93].

Aspirin, at present the drug of choice for prevention of cardiovascular events, irreversibly blocks platelet cyclooxygenase-1, which inhibits the production of tromboxane A2 resulting in a decreased platelet aggregation. Two large meta-analyses both showed a reduction of major vascular mortality and cerebro- and cardiovascular events in patients with PAD using aspirin [94, 95]. Therefore it is recommended that all symptomatic patients with PAD must be prescribed an anti-platelet drug [4, 17, 18, 63, 93].

Exercise rehabilitation

The cornerstone treatment of patients with PAD is exercise rehabilitation. Exercise rehabilitation showed to improve walking distance, quality of life and improvement of carotid and coronary arthrosclerosis and cardiovascular morbidity and mortality [2, 16, 18, 96-102]. Although unsupervised home-based exercise therapy does have effect, supervised exercise therapy is superior [16, 98, 103]. There are different programs available, although the optimal exercise program is not defined yet.

The pathophysiology behind the improvement in walking performance resulting from exercise training is still unclear. Different mechanisms have been proposed. First, it has been suggested that overall improvement of cardio-pulmonary condition related to exercise could be one of the mechanisms [102, 104, 105]. However, several studies have found no or only very small improvement in the physical adaptations to exercise [102, 104, 105]. Second, it was thought that exercise training enhances collateral blood supply, resulting in an increased blood supply after the stenosis [102]. However, although this is at the moment still the running theory, several studies did not find an increased blood supply after exercise training [2, 98, 102, 105-107]. A third mechanism to explain the increased walking performance is an improvement in endothelial function [2, 108, 109]. Improvement in vascular endothelial function after exercise training was confirmed by Andreozzi et al [108]. They found that after supervised training of three times a week during 6 weeks resulted in an improvement of resting and exercise vascular endothelial function.

Revascularisation

In patients with PAD unresponsiveness to: the current known medical therapies, as displayed above, exercise rehabilitation or patients with critical limp ischemia, revascularisation therapy (endovascular or surgical|) must be considered [16, 18]. Depending the site, type and severity of the lesion and co-morbidities of the patient, endovascular therapy is the therapy of choice [16, 18].

Treatment of patients with ABI ≥ 0.90

In patients with resting ABI above 0.90 but with abnormal exercise test results, optimal medical treatment is unknown and hardly investigated yet. All the above described interventions are studied in patients with PAD. However, one could hypothesise that the

same pathophysiology plays an important role in patients with already established PAD, although the disease is probably still in an earlier stage. It could be imaged that these patients in particular will benefit from early treatment. Further research is needed to investigate which and when treatment is needed to improve the long-term outcome in these patients.

CONCLUSION

Treadmill exercise test parameters are important to identify patients with increased mortality risks, which might otherwise remain unrecognised and untreated. Besides risk stratification, exercise tests could also be used to identify patients with progressive PAD, or to evaluate treatment effects. Nevertheless, further research is needed to investigate which and when treatment is needed to lower morbidity and mortality in patients subclinical and already established PAD.

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Summary and Conclusions

11

SUMMARY AND CONCLUSIONS

In this thesis, the clinical prognostic value of treadmill exercise testing in patients with known or suspected PAD, is described.
According to the guidelines, a resting ABI < 0.90 is defined as PAD [1-5]. Nevertheless, due to the fact that the ankle systolic blood pressure is normally higher than the systolic blood pressure at the arm, values of less than 1.10 should be considered as abnormal [6]. In general, the ABI measurement at rest is most often used to diagnose PAD, especially in the primary care practise [7, 8]. However, in **chapter 2** we showed 85% of the patients with a resting ABI ≥ 0.90, had an ABI < 1.1 after the exercise test and even 35% had an ABI < 0.90. This impaired exercise ABI was especially found in patient who were 50 years or older and having hypertension. Additionally, we observed that an impaired exercise ABI turned out to be associated with an adverse outcome. The lower the exercise ABI value was, the worse the outcome became. Therefore, we recommend that at least patients with a resting ABI ≥ 0.90, who are 50 years or older and having hypertension should undergo treadmill exercise testing.

In **Chapter 3,4** and **5** we described the association of an abnormal blood pressure response during the treadmill exercise test and long-term outcome. Both a hypotensive blood pressure response and a hypertensive blood pressure response were strongly associated with a higher cerebrovascular and cardiac event rate and higher mortality rate [9, 10]. In patients with a hypertensive blood pressure response statins, beta-blocker and aspirin use might reduce these risks [9]. Also in patients with a hypotensive blood pressure response these medications showed a positive effect on long-term outcome as well [10]. We further investigated the association between these abnormal blood pressure responses and perioperative complications after major elective vascular surgery. It showed us that patients with a hypertensive blood pressure response had an increased risk of perioperative thrombectomy, but not for perioperative cardiac complications. In contrast, patients with a hypotensive blood pressure response were at an increased risk of myocardial infarction and other cardiac complications and death, when compared to patients with a normal blood pressure response. However, this is a retrospective study and additional research is needed to confirm our results.

The walking distance at the treadmill exercise test was investigated in the **chapters 6,7 and 8**. In our study we observed that in both, patients with a normal resting ABI and patients with an impaired ABI, an impairment in the total walking distance was independently associated with a higher mortality rate [11]. We additionally observed that in patients with and without abnormal ABI, impairment in walking distance was associated with impairment in their quality of life. This illustrates that walking impairment is an important

prognostic indicator of adverse long-term outcome in both patients with already established or suspected PAD. Therefore, an impaired walking distance might be a warning sign for physicians to monitor these patients more carefully and to provide them optimal treatment. Furthermore, we showed that the exercise test can not only be used for diagnostic purposes and risk stratification but also as a tool to monitor the progression of the disease [12]. In a subgroup of patients in whom multiple exercise tests were performed but didn't undergo surgery between the tests, we observed that a decrease in walking distance was strongly related with a higher long-term mortality rate independent of clinical risk factors and ABI [12]. This decline in walking distance probably reflects the progression of the systemic arteriosclerosis although, to our knowledge, there are no studies yet to confirm our findings with quantitative measurements.

After we explored the prognostic values of the individual exercise test parameters, we investigated the prognostic value of the combination of the different treadmill exercise parameters together **(chapter 9)**. In patients with resting ABI ≥ 0.90, we observed that both exercise ABI and walking distance added significant prognostic value, but an abnormal blood pressure response did not. In contrast to the patients with an exercise ABI ≥ 0.90, patients with a resting ABI < 0.90, both an impaired walking distance and an abnormal blood pressure response added significant additional value on long-term outcome, but exercise ABI did not. We further observed that the mortality rate increases when more exercise tests parameters became abnormal, with the highest mortality risk in patients with a resting ABI <0.90 with both a walking distance impairment and an abnormal blood pressure response.

In conclusion, besides for diagnostic purposes, treadmill exercise testing in patients with known or suspected PAD, provide a large amount of important clinical variables. These variables could play an essential role in identifying patients with increased risk of a worse long-term outcome, who otherwise might remain unrecognised and untreated. Additionally, these exercise tests could also play an important role to monitor the progression of the peripheral arterial disease.

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SAMENVATTING EN CONCLUSIES

Dit proefschrift beschrijft het belang van de inspanningstest bij patiënten met of die verdacht worden van perifeer vaatlijden.

Perifeer vaatlijden is een manifestatie van systemische arteriosclerose [1-6]. Deze ziekte komt bij miljoenen mensen voor. Afhankelijk van de onderzoekspopulatie worden in de literatuur prevalenties tussen de 4% en 29% genoemd [1,7]. Alarmerend is, dat men verwacht dat deze aantallen in de komende jaren zullen stijgen omdat de risicofactoren voor deze ziekte zoals suikerziekte, overgewicht en gebrek aan beweging toenemen [1,6,7]. Patiënten met perifeer vaatlijden hebben een verhoogd risico op cardiovasculaire morbiditeit, sterfte, hebben sterke beperkingen in hun fysieke functioneren, met name lopen, en geven in onderzoeken aan een slechtere kwaliteit van leven te hebben ([3,4,8-18]). In verband hiermee is het belangrijk de diagnose vroeg in het ziekteproces te diagnosticeren, om snel en zo optimaal mogelijk te kunnen behandelen om daarmee hopelijk de comorbiditeit te kunnen verlagen.

Helaas zijn de symptomen van dit ziektebeeld erg variabel. Het klassiek symptoom, pijn in de benen bij inspanning welke met rust weer verdwijnt, komt slechts bij een minderheid voor [6,19,20]. Uit onderzoek is gebleken dat de symptomen sterk kunnen variëren, waarbij 20% tot 50% van de patiënten helemaal geen klachten heeft [2-4, 6, 19-26].

Voor de diagnose perifeer vaatlijden wordt de enkel arm index (ankle brachial index = ABI) gebruikt. Dit is de ratio tussen de systolische bloeddruk aan de enkel ten opzichte van de systolische bloeddruk aan de arm [3-5,27]. Waardes onder de 0.90 zijn geassocieerd met een vernauwing van dan bloedvaten van meer dan 50% [4]. Daarnaast zijn er verbanden gevonden tussen de ABI, cardiovasculaire morbiditeit en sterfte, en de ABI kan daarnaast gebruikt worden voor prognostische risicostratificaties [1, 9, 28].

Hoewel inspanningstesten in de praktijk wel worden verricht, verloopt de meting van de ABI om perifeer vaatlijden the diagnostiseren meestal in rust, vooral in de eerste lijn. Volgens de richtlijnen wordt perifeer vaatlijden gedefinieerd als een rust ABI < 0.90 [1,4, 8, 9, 28]. Maar uit recente literatuur blijkt dat een rust ABI < 1.1 al afwijkend kan zijn [29]. De inspanningstesten worden voornamelijk in vaatlaboratoria uitgevoerd onder begeleiding van speciaal opgeleid personeel. Bij een dergelijk inspanningstest moeten patiënten 5 minuten op een loopband lopen terwijl er allerlei parameters zoals de inspanning ABI, loopafstand en bloeddruk gemeten worden. Uit ons onderzoek in **hoofdstuk 2** is gebleken dat 85% van de patiënten met een rust ABI ≥ 0.9, na de inspanningtest een ABI< 1.10 hadden en 35% zelfs een ABI <0.90. Deze verminderde inspanning ABI was vooral te zien bij patiënten van 50 jaar en ouder en bij patiënten met hypertensie. Daarnaast bleek dat hoe slechter de inspanning ABI was hoe slechter de overleving. Op basis van deze resultaten adviseren wij dat minimaal alle naar een vaatlaboratorium verwezen patiënten

met een rust ABI > 0.90 en die ten minste 50 jaar oud zijn en hypertensie hebben, een inspanningstest moet ondergaan.

In de **hoofdstukken 3,4 en 5** omschrijven we het effect van een abnormale bloeddruk reactie bij de inspanningstest. Tijdens inspanning behoort de systolische bloeddruk iets te stijgen [30]. Nu zijn er patiënten waarbij de systolische bloeddruk tijdens de inspanning t.o.v de bloeddruk in rust daalt (hypotensieve bloeddrukreactie). Bij hartpatiënten is dit een bekend fenomeen en zou mogelijk geassocieerd zijn met ernstig vaatlijden aan de kransslagaders van het hart [31-34]. De consequenties van deze hypotensieve bloeddruk reactie zijn echter niet of nauwelijks onderzocht bij patiënten met perifeer vaatlijden. Daarnaast zijn er ook patiënten die tijdens een inspanningstest een uitzonderlijk hoge bloeddruk krijgen (hypertensieve bloeddruk reactie). Ook hierover is nog nauwelijks iets bekend in de literatuur. Uit onze resultaten is gebleken dat zowel de hypotensieve als de hypertensieve bloeddruk reactie tijdens de inspanningstest sterk geassocieerd zijn met een verhoogd risico op cardiale en cerebrale events en sterfte [35,36]. Gelukkig hebben statines, beta-blokkers en aspirine een gunstig effect op deze verhoogde risico's in zowel patiënten met een hypertensieve als met een hypotensieve bloeddruk reactie [35,36]. In **hoofdstuk 5** hebben we onderzocht of deze patiënten met een abnormale bloeddrukreactie ook een verhoogd risico hebben op post operatieve complicaties na een grote electieve vaatchirurgische operatie. Uit onze resultaten kwam naar voren dat patiënten met een hypertensieve bloeddruk reactie een verhoogd risico hadden op een postoperatieve trombectomie, maar geen verhoogd risico op postoperatieve cardiale complicaties. Dit is in tegenstelling tot patiënten met een hypotensieve bloeddruk reactie. Zij hadden wel een verhoogd risico op postoperatieve hartinfarcten, cardiale complicaties en sterfte. Nu moet er wel bij vermeld worden dat dit een retrospectief onderzoek is en dat aanvullend onderzoek nodig is om deze resultaten te bevestigen.

De loopafstand tijdens de looptest is onderzocht in de **hoofdstukken 6,7, en 8.** Daarbij vonden we dat een verminderde loopafstand, bij zowel de patiënten met een normale ABI als bij patiënten met een abnormale ABI (< 0.90), sterk geassocieerd is met een verhoogde sterfte op de lange termijn, onafhankelijk van andere bekende risicofactoren [37]. Tevens ontdekten we dat deze loopafstand ook een relatie heeft met de kwaliteit van leven. Deze studies geven dus aan dat een verminderde loopafstand tijdens een inspanningstest belangrijke prognostische waarde heeft voor de uitkomst op lange termijn. Een verminderde loopafstand is dus een belangrijk waarschuwingsteken voor de behandelende arts om deze patiënten goed in de gaten te houden en zo optimaal mogelijk te behandelen. Daarnaast hebben we in **hoofdstuk 8** laten zien dat de looptesten niet alleen voor diagnostiek en risico stratificatie gebruikt kunnen worden, maar ook om de progressie van het ziektebeeld aan te tonen [38]. In ons onderzoek vonden wij dat als de loopafstand tussen twee looptesten

achteruitgaat de sterfte ook sterk omhoog gaat. Dit geeft waarschijnlijk aan dat de ziekte progressief is. Helaas zijn er, zover bij ons bekend, tot op heden geen studies verricht die deze progressie ook daadwerkelijk kwantitatief hebben gemeten.

Vervolgens, na alle parameters van de inspanningstest onafhankelijk van elkaar te hebben bekeken, hebben we de voorspellende waarde van alle parameters (rust ABI, inspanning ABI, abnormale bloeddruk reactie en loopafstand gezamenlijk) samen onderzocht. Dit onderzoek wordt besproken in **hoofdstuk 9.** Hier laten we zien dat bij patiënten met een normale rust ABI, de inspanning ABI en de loopafstand, maar niet de bloeddruk reactie, extra informatie oplevert over het sterfterisico t.o.v de al bekende risicofactoren. Daarentegen gaf bij patiënten met een abnormale rust ABI zowel de loopafstand als de bloeddruk reactie extra informatie maar niet de inspanning ABI. Daarnaast zagen we dat hoe meer inspanningstest parameters afwijkend werden hoe hoger de sterfte op lange termijn. De hoogste sterfte werd gezien in patiënten met een abnormale rust ABI, een abnormale bloeddruk reactie en verminderde loopafstand.

Concluderend, hoewel inspanningstesten tot nu toe voornamelijk gebruikt worden voor diagnostische doeleinden, geven deze inspanningstesten voor patiënten met of die verdacht worden van perifeer vaatlijden vele klinische parameters. Deze parameters kunnen een belangrijke rol kunnen spelen in het identificeren van patiënten met verhoogde risico's op morbiditeit en sterfte, die mogelijk anders onopgemerkt zouden blijven. Daarnaast kunnen deze inspanningtesten ook een belangrijke rol spelen voor de monitoring van de progressie van de ziekte.

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de Liefde II, van Dijk M, Tibboel D, Bosenberg A. Epidural analgesia in neonates: a worthwhile alternative? *Canadian Journal of Pain Research & Management, Summer 2006, Volume 11, Supplement: 1B-93B*

de Liefde II, van der Klift M, de Laet CE, van Daele PL, Hofman A, Pols HA. Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. *Osteoporos Int. 2005 Dec;16(12):1713-20*

de Liefde II, van der Klift M, de Laet CE, van Daele PL, Hofman A, Pols HA. Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. *JBMR Vol 18 Suppl 2 Sept 2003, pS8.*

PRESENTATIONS

de Liefde II, Welten GMJM, Klein J, van Domburg RT, Verhagen HJM, Stolker RJ, Poldermans D Increased perioperative complications after major vascular surgery in patients with a preoperative abnormal exercise blood pressure response. *Wetenschapsdag, 09-2010, poster discussion*

de Liefde II, van Domburg RT, Klein J, Bax JJ, Verhagen HJM, Poldermans D. Exercise ankle brachial index add important prognostic information on long-term out-come in patients with normal resting ankle brachial index. *Stockholm, European Society of Cardiology, 09-2010, oral presentation*

de Liefde II, Welten GMJM, Klein J, van Domburg RT, Verhagen HJM, Stolker RJ, Poldermans D Increased perioperative complications after major vascular surgery in patients with a hypertensive or hypotensive exercise blood pressure response. *Stockholm, European Society of Cardiology, 09-2010, poster*

de Liefde II, Hoeks SE, van Gestel YRBM, Klein J, Bax JJ, Verhagen HJM, van Domburg RT, Poldermans D. Impaired walking distance is a strong prognostic indicator on long-term outcome in both patients with impaired and normal ABI. *Barcelona, European Society of Cardiology, 09-2009, oral presentation*

de Liefde II, Hoeks SE, Smolderen KG, Klein J, Bax JJ, Verhagen HJM, van Domburg RT, Poldermans D. Walking performance predicts long-term health in patients with normal or impaired ankle brachial index. *Barcelona, European Society of Cardiology, 09-2009, poster*

de Liefde II, Hoeks SE, Smolderen KG, Klein J, Bax JJ, Verhagen HJM, van Domburg RT, Poldermans D. Improvement in walking performance affects long-term quality of life in non-vascular peripheral artery patients. Barcelona, *European Society of Cardiology, 09-2009, poster*

de Liefde II, van Gestel YRBM, Dunkelgrun M, Feringa H, Azizi F, van Domburg RT, Klein J, Poldermans D. Hypotensive response after treadmill exercise test for peripheral arterial disease is associated with an increased risk of long-term mortality. *Vienna, European Society of Cardiology, 09-2007, oral presentation*

de Liefde II, Hoeks SE, Dunkelgrun M, Feringa H, Azizi F, van Domburg F, Klein J, Poldermans D. Exaggerated blood pressure response during exercise test for peripheral arterial

disease predicts 10-year mortality: a prospective cohort study in 2110 patients. *Vienna, European Society of Cardiology, 09-2007, oral presentation*

de Liefde II, van Dijk M, Tibboel D, Bosenberg A. Epidural analgesia in neonates: a worthwhile alternative? *Vancouver, International symposium on Pediatric Pain, 6-2007, poster*

de Liefde II, van der Klift M, de Laet CE, van Daele PL, Hofman A, Pols HA. Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. *Minneapolis, Annual meeting of the ASBMR, 6-2005, poster*

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student: Inge I de Liefde
Erasmus MC Department: Anesthesiology
Research School: Erasmus MC

PhD period: 2006-2011
Promotor(s): Prof. dr. Poldermans

1. PhD training

	Year	Workload (ECTS)
General courses		
- NIHES, MSc clinical epidemiology	2001-2003	70
Specific courses (e.g. Research school, Medical Training)		
- Working with SPSS for windows	2002	2
- Introduction to medical writing	2003	0.3
Seminars and workshops		
- Harvard School of public health: priniciples of epidemiology / Management Health care organisation	2003	8
- Communication	2007	0.3
- Hospital management	2009	0.6
- Negotiating	2009	0.3
- Cooperation	2009	0.3
Presentations		
- National conferences	2010	1
- International conferences	2005-2010	9
(Inter)national conferences		
- Annual meeting of the ASNMR, Minneapolis	2005	1
- International symposium on Pediatric Pain	2007-2010	1
- European Society of Cardiology Congress, annual	2007-2010	3
- Wetenschapsdag anesthesiologie	2010	1

2. Teaching

	Year	Workload (ECTS)
Lecturing		
- Clinical training for nurses	2007	0.6
Supervising practicals and excursions, Tutoring		
- Tutoring nurse anesthetist	2007-2008	1