Patient profiles and outcomes in lower-extremity peripheral arterial disease

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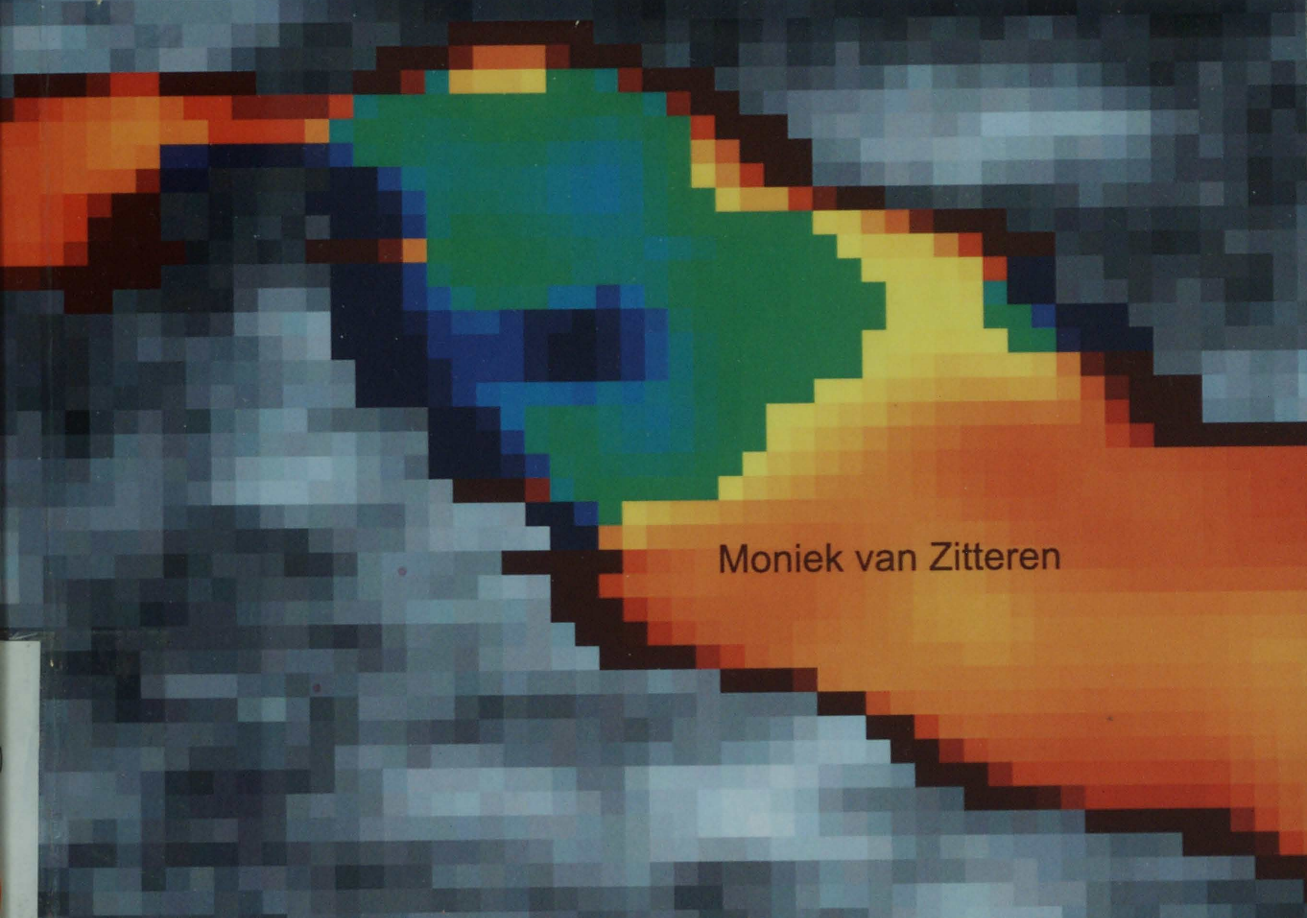
Towards a Patient-Centered Approach



Moniek van Zitteren

Patient Profiles and Outcomes in Lower-Extremity Peripheral Arterial Disease: Towards a Patient-Centered Approach

Moniek van Zitteren

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Patient Profiles and Outcomes in Lower-Extremity Peripheral Arterial Disease: Towards a Patient-Centered Approach

PROEFSCHRIFT

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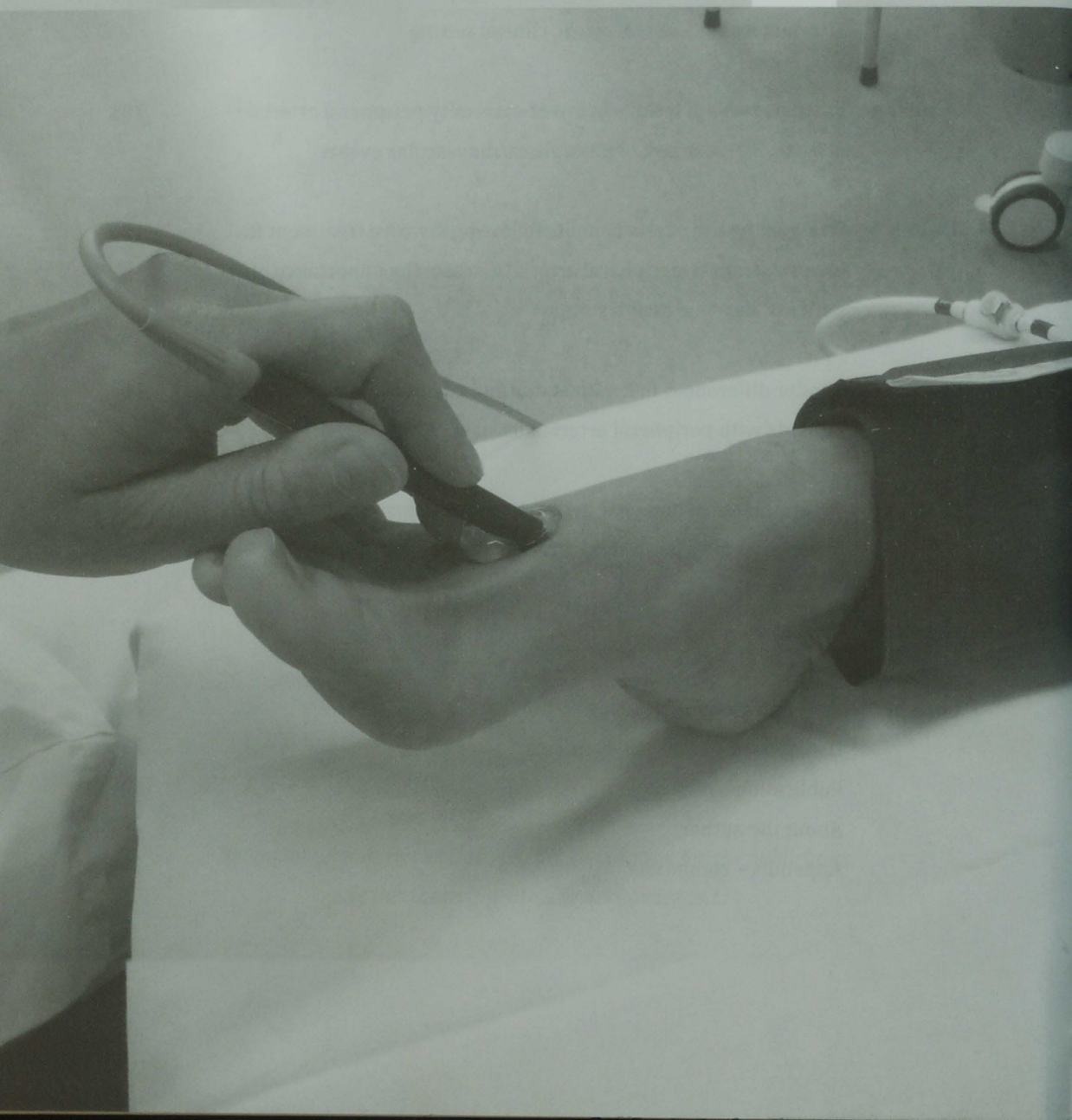
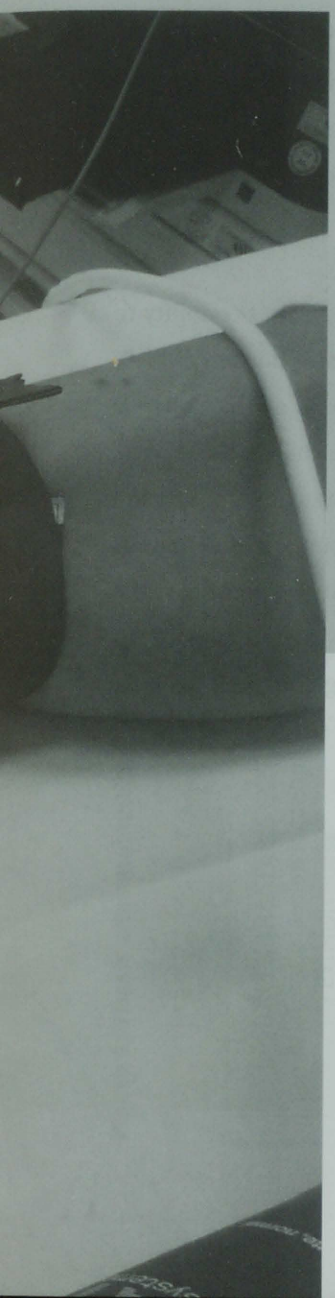
Chapter 1



Introduction



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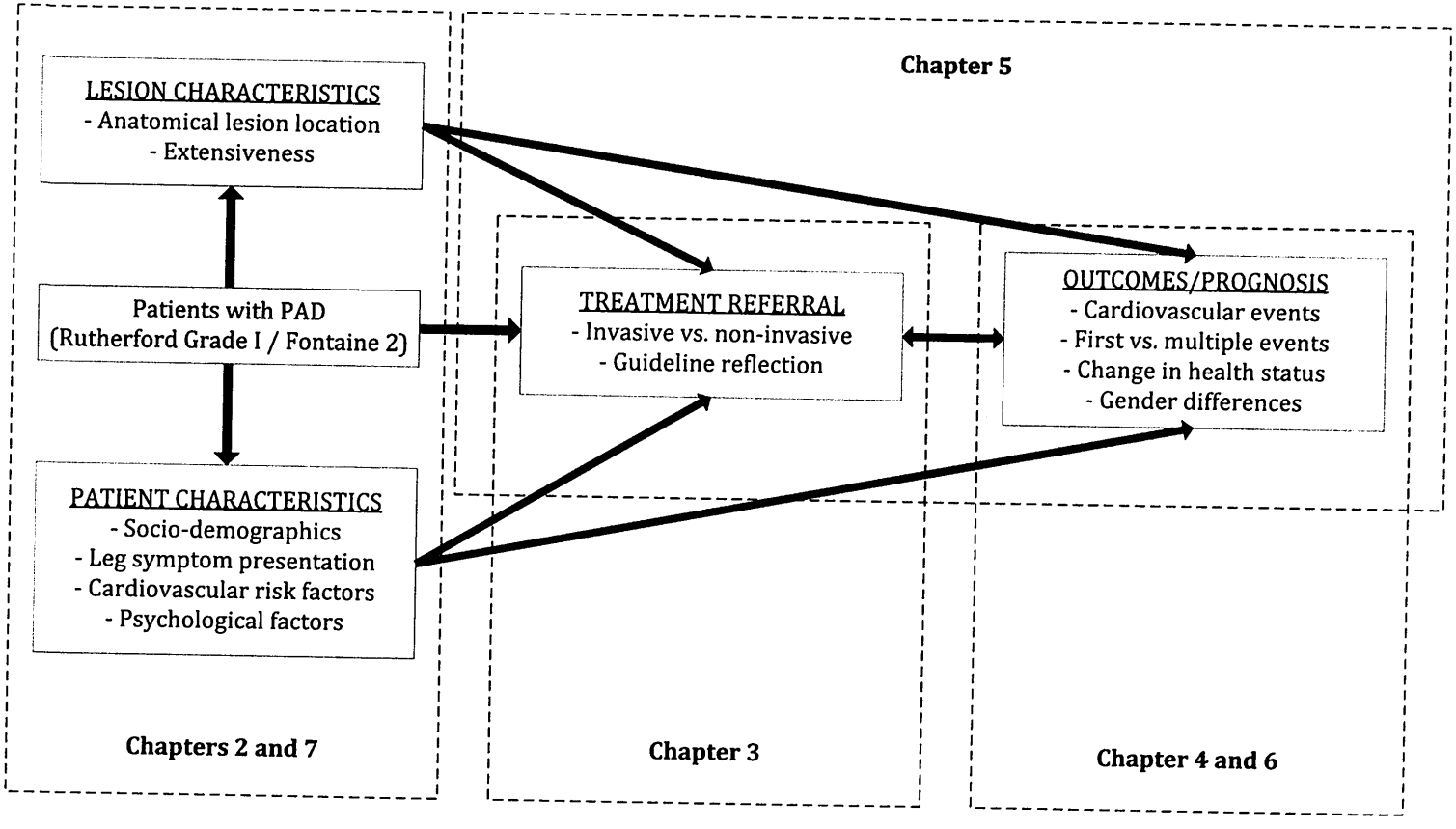
INTRODUCTION

Patients with lower-extremity peripheral arterial disease (PAD) comprise a vulnerable population because they experience a substantial disease burden due to a diminished blood supply to their lower-extremity arteries. Besides functional impairments from the inability to walk distances and exertional leg pain, patients also experience a diminished health status burden, quality of life, and psychological well-being.[1-11] Patients undergo lower-extremity procedures with the goal to alleviate their symptoms and to improve their quality of life.[4, 5, 12, 13] In addition, because of the generalized nature of atherosclerosis – also affecting the coronary and carotid arteries[14-16] – these patients are facing increased risks of experiencing adverse cardiovascular events and mortality.[14-18] Despite patients' personal health burden of PAD, this manifestation of atherosclerosis has an effect on the public health care burden when considering social and economic implications.[15]

Because multiple gaps in the current knowledge of PAD exist that may limit the ability to improve patient-centered outcomes and that may lower the health care burden of PAD, this chapter (*Chapter 1*) will first provide an overview on the clinical aspects of PAD such as patients' clinical presentation, the anatomical lesion location they present with, and guideline recommended care. The rationale for this thesis and several gaps in the current knowledge of PAD will then be discussed focusing on various major themes including the documentation of PAD subpopulations, risk stratification initiatives, the clinical decision-making process, and (patient-centered) outcomes in PAD (Figure 1). Finally, *Chapter 1* clarifies how the identified gaps in knowledge of PAD will be addressed by the following *Chapters*.

Figure 1. Thesis aims and outline.



1.1. The clinical presentation of lower-extremity peripheral arterial disease

Lower-extremity peripheral arterial disease (PAD) is a manifestation of generalized atherosclerotic plaque formation that causes partial or complete obstruction of the lower-extremity arteries distal to the aortic bifurcation.[19] The clinical presentation of PAD is diverse and covers a wide spectrum of different gradual disease stages (Table 1). Patients can either be asymptomatic (Fontaine 1) or gradually present with typical or atypical leg symptoms. More than half of the PAD population has symptomatic disease (Fontaine 2-4), and experiences leg pain, fatigue or discomfort during exercise that is relieved upon rest (Fontaine 2).[4, 20, 21] This classical presentation of PAD – intermittent claudication – is present in approximately one third of patients with symptomatic PAD,[20, 22] whereas the majority presents with atypical exertional leg symptoms. The atypical symptom presentation might initially be confused with neurologic or orthopedic conditions, resulting in an underestimation of the true prevalence of PAD and potential delay of patients' diagnosis.[20, 21] Men are more likely to present with intermittent claudication while atypical symptoms are more often seen in women.[23] Figure 2 displays an overview of the typical vs. atypical symptom presentation in PAD based on the Rose criterion for claudication[24] and the San Diego Claudication Questionnaire.[25]

A substantial number of patients with symptomatic PAD (10-50%) will never consult a doctor for their symptoms,[5] but the majority undergoes a clinical evaluation at vascular outpatient clinics – before their symptoms progress to ischemic pain at rest (Fontaine 3) or ischemic gangrene and ulcers (Fontaine 4).[4, 5] Identifying patients with PAD at an early stage is important to assign adequate treatment to prevent disease progression and to prevent adverse cardiovascular outcomes.[4, 5, 13] This thesis will further focus on symptomatic patients with PAD presenting with typical as well as atypical exertional leg symptoms (Fontaine 2).

Table 1. Categorization of lower-extremity peripheral arterial disease by Fontaine and Rutherford.

Fontaine stages		Rutherford categories		
Stage	**Clinical presentation**	**Grade**	**Category**	**Clinical presentation**
I	Asymptomatic	0	0	Asympatomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate-severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic pain at rest	II	4	Ischemic pain at rest
IV	Ulceration or gangrene	III	5	Minor tissue loss
		IV	6	Ulceration or gangrene

Adapted from Dormandy J.A. et al. J Vasc Surg 2000.[26]

1.1.1. Epidemiology and risk factors

PAD – an expression of atherosclerosis in the lower-extremity arteries – is prevalent in 3-10% of the general population as assessed by the Rose Claudication criterion or non-invasive measurements (i.e., ankle-brachial index [ankle blood pressure divided by brachial blood pressure], pulse palpation, segmental blood pressure).[25, 27] The prevalence increases substantially with age (≥20% in those over the age of 70).[5, 25, 27-29] Risk factors for the development of PAD are the same as the classical risk factors that are related to atherosclerosis presenting in the coronary or carotid arteries and include older age, male gender, cigarette smoking, the presence of hypertension, dyslipidemia, diabetes mellitus, and hyperhomocysteinemia.[4, 5] In addition, patients from other ethnicities (i.e., Black/African American) are more prone to develop PAD and to present with more severe PAD as compared with Caucasians.[5, 30-33] Finally, the presence of elevated inflammatory markers (C-reactive protein), hyperviscosity, and chronic renal dysfunction also increase patients' risks for developing PAD.[5]

1.1.2. Diagnosis

Clinical evaluation and ankle-brachial assessments

Most patients who are evaluated for PAD in the Netherlands are being referred to vascular surgeons after an initial evaluation by their general practitioners[34] or other medical specialists. This is different from other countries where patients with PAD are additionally being evaluated and treated by interventional cardiologists, interventional radiologists, or vascular medicine specialists. Patients with symptoms of PAD will undergo a clinical evaluation that usually includes a non-invasive assessment of patients' ankle-brachial indices (ABI). Assessment of patients' ABI is the most important diagnostic instrument to objectively diagnose the presence of PAD and can additionally be used to monitor treatment effects.[4, 5, 12] For ABI assessments, the systolic blood pressure of both brachial arteries, posterior tibial arteries and dorsalis pedis arteries is measured at rest and again following a treadmill exercise test. The ABI is calculated by dividing the highest ankle pressure in each leg by the highest brachial pressure. A resting ABI of ≤ 0.90 or post-exercise decrease by at least 15% is indicative of PAD.[4, 5, 35] When using a threshold of 0.90, the ABI has 95% sensitivity and 100% specificity as compared with angiography to detect the presence of PAD.[4, 36]

Radiological assessments of arterial lesion information

While additional radiological assessments are not part of a standard diagnostic work-up in each vascular clinic, they can be performed in patients having an abnormal ABI. Radiological imaging can additionally assess the anatomical location, severity, and extensiveness of lower-extremity arterial lesions (i.e., atherosclerotic plaque formation resulting in significant stenoses or occlusions) to plan future interventions or monitor disease progression.[4, 5, 12, 13] Such information can be derived from various radiological imaging techniques that have been frequently used such as duplex ultrasound testing (DUS), magnetic resonance angiography (MRA), computed tomography angiography (CTA), and digital subtraction contrast angiography. Although all techniques have the ability to detect significant lower-extremity arterial lesions, to determine the anatomical location, and to assess lesion severity, each one of them has its own limitations and benefits in detecting significant arterial lesions.

While DUS, MRA, and CTA are useful to select candidates for lower-extremity revascularization,[4, 5] gold standard digital subtraction contrast angiography can serve as a diagnostic modality where additional revascularization can be performed simultaneously.[4, 5] In addition, DUS can be used to monitor venous graft patency, but might be limited in detecting aortoiliac lesions (e.g., in obese patients or when bowel gas is present), when arteries are extremely calcified or when more downstream lesions are present.[4, 5] The MRA technique for detecting significant lesions could overestimate lesion severity and might be inaccurate in arteries that have been treated with metal stents.[4] Furthermore, various contraindications may limit the use of MRA (e.g., pacemaker, or intracranial metal stents, clips/coils, claustrophobia). CTA can be performed in patients with contraindications for MRA and in a faster way, but intravenous contrast agents are mandatory limiting its usefulness in patients with renal dysfunction.[4] Digital subtraction contrast angiography has been considered as gold standard for detecting significant lesions in PAD. Angiography is usually combined with an intervention, such as balloon angioplasty and stenting. The diagnostic value is specifically high in distal arteries, but numerous projections are needed.[4] Several risks and complications (e.g., risk of bleeding, vascular access complications, contrast allergy or nephropathy, and infections) accompany this invasive diagnostic modality.[4]

Part of the work that has been performed in this thesis is based on the anatomical location as well as the extensiveness of lower-extremity arterial lesions and was assessed by symptom-driven duplex ultrasound testing to systematically categorize patients into anatomical lesion location categories on the one hand and extensiveness categories on the other hand. The duplex ultrasound examination protocol and categorization of anatomical lesions have been described in full detail in *Chapter 2*.

1.1.3. Concomitant vascular disease and prognosis

Due to the generalized nature of atherosclerosis, it is not surprising that lower-extremity PAD is associated with concomitant coronary artery disease (CAD) and cerebrovascular disease (CVD).[14-16] Prior registries demonstrated that polyvascular disease (i.e., PAD with CAD and/or CVD) is present in 70% of patients with established PAD.[15] As a consequence, patients with PAD not only experience physical impairment and a reduced quality of life due to leg symptoms, but they also have an increased risk of adverse cardiovascular events and mortality and repeated vascular interventions.[6, 7, 10, 14-16, 18]

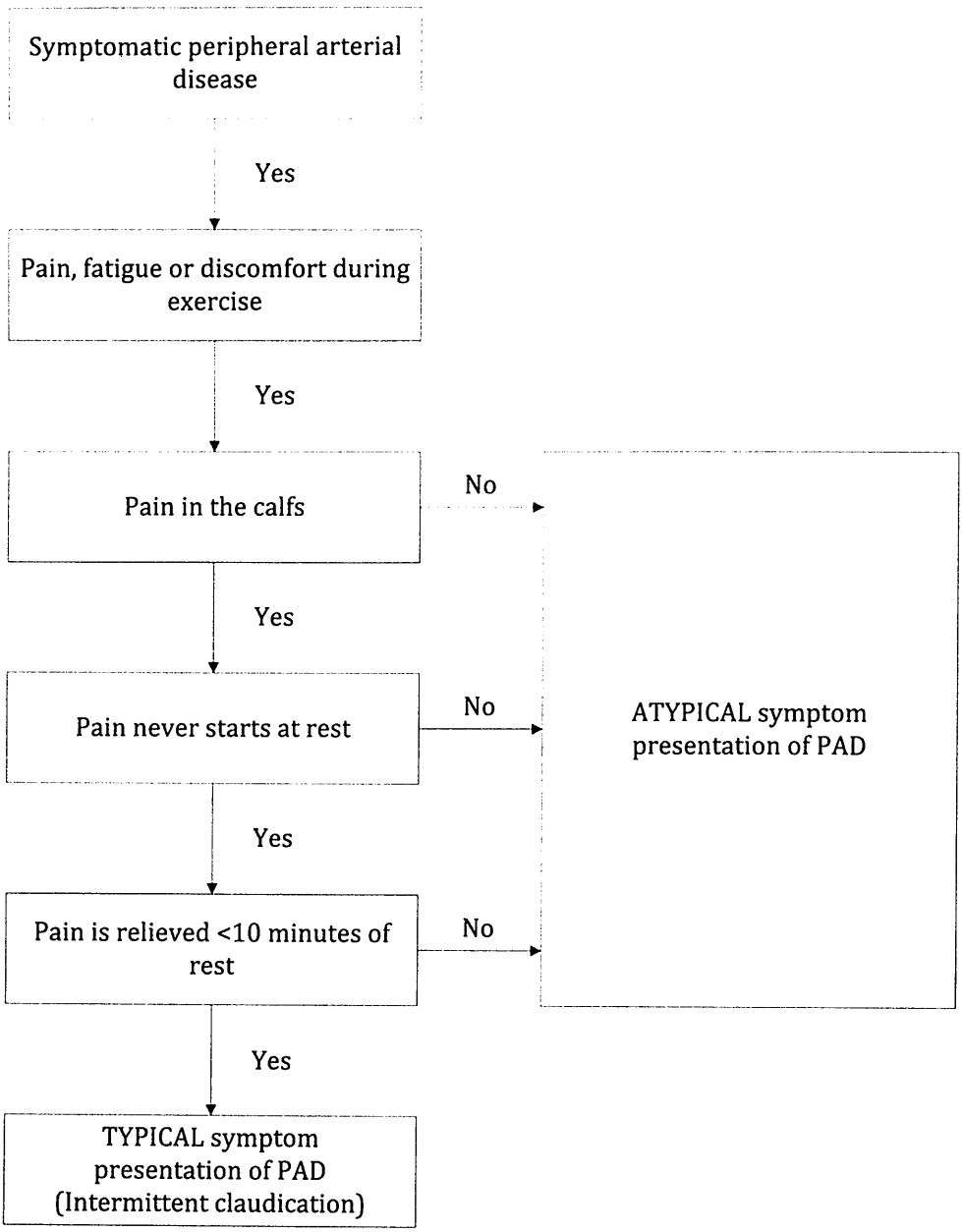
One fifth of patients with PAD will experience at least one cardiovascular event and 15-30% will die within 5 years after the initial diagnosis.[4, 37, 38] In addition, patients with polyvascular disease have a twofold increased risk of cardiovascular death, myocardial infarction or stroke as compared with those only having classical risk factors.[14] In contrast, only 10-20% of all patients experience symptom progression and a minority (1-2%) progresses to critical limb ischemia with the risk of limb amputation.[4] These figures illustrate the importance to acquire novel insights in this vulnerable population in order to forestall disease progression, to prevent adverse events, and to diminish patients' health care burden.

1.1.4. Diminished health status in peripheral arterial disease

Apart from patients' functional abilities, their lower-extremity symptoms may also impact their health status as well as their psychological well-being.[1-7, 10, 11] Health status has been investigated in more detail in cardiac populations,[39-41] but this phenomenon remains less well documented in PAD.[10] Prior findings suggest that having a poorer health status was associated with higher mortality rates and hospitalizations in cardiac populations.[3, 39-41] In addition, it is suggested that patients' health status remains impaired even after undergoing a successful endovascular revascularization procedure.[6, 10, 42]

These observations emphasize that patients' health status should be taken into account in the medical decision-making process for treatment referral and that these decisions should not be solely based on clinical determinants. The treatment goal of PAD is to improve patients' health status and to prevent adverse outcomes.[4, 5, 12, 13] In an era where patient-centered outcomes are becoming increasingly important, there is a real need to document patients' psychological burden in addition to their medical condition.

Figure 2. Flowchart for typical vs. atypical symptom presentation in peripheral arterial disease. Based on the Rose criteria for claudication[24] and the San Diego Claudication Questionnaire.[25]



Abbreviation: PAD = peripheral arterial disease.

1.2. Characteristics of lower-extremity arterial lesions

1.2.1. Anatomy of the lower-extremity arteries

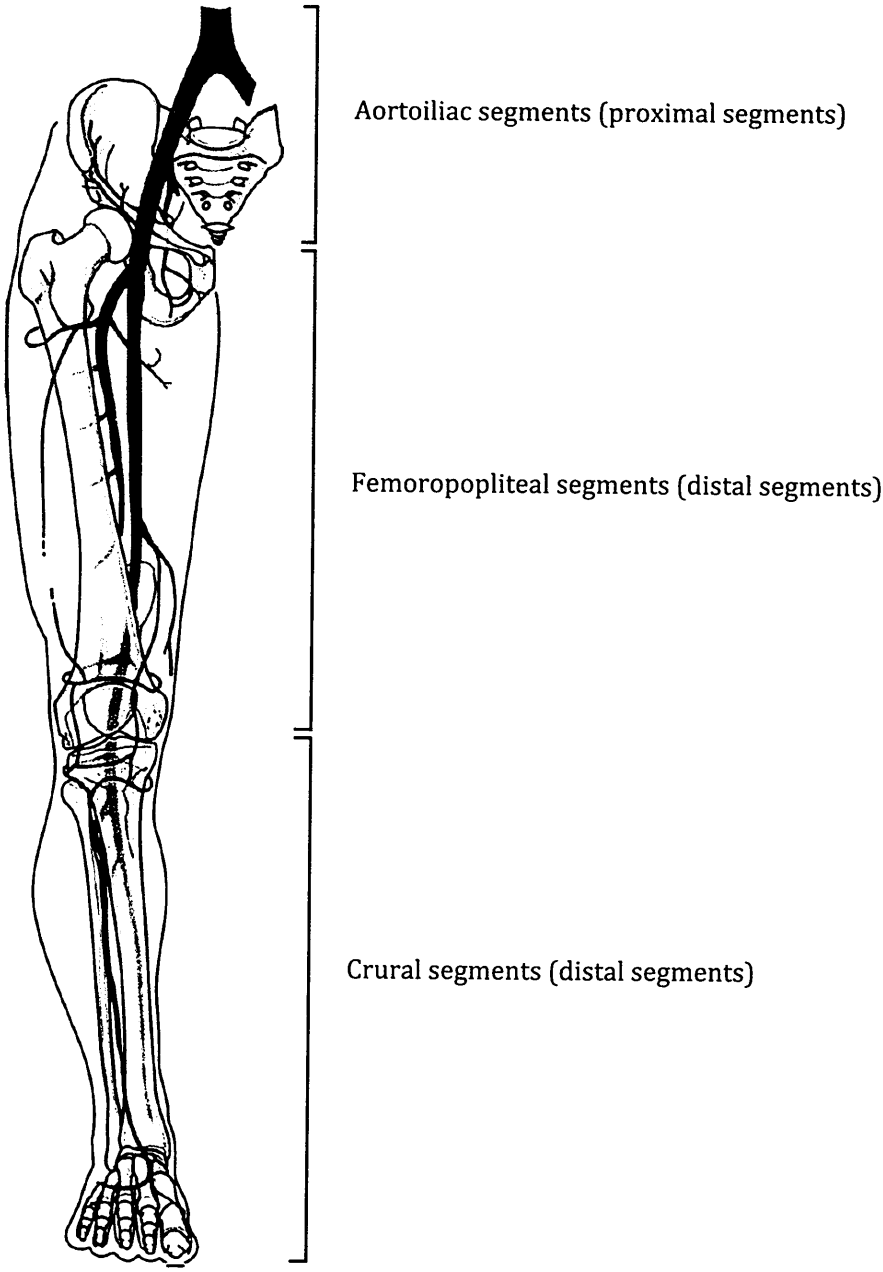
The lower-extremity arteries originate from the distal part of the aortic bifurcation where the aorta separates into the left and right *iliac arteries* and can be followed down to the foot arteries.[17] At the level of the groins, the external iliac artery branches of into the common femoral artery that introduces the beginning of the *femoropopliteal arteries*.[17] Finally, the *crural arteries* are located below the level of the knee. Although consensus in the terminology of *large* and *small* vessels is lacking,[43] the aortoiliac segments are often being referred to as *proximal* or *large* vessels, whereas the femoropopliteal and crural segments are being referred to as *distal* or *small* vessels (Figure 3).[17, 43]

1.2.2. Anatomical location and extensiveness of lower-extremity arterial lesions

While it is known that atherosclerosis typically is systematically distributed across the arterial system, prevalence rates of arterial lesions vary among vessels.[44] For example, the superficial femoral artery is most commonly affected as compared with aortoiliac arteries.[44] Despite this observation, it remains unclear why atherosclerosis is predominantly present in certain arteries, and not in others.[44] Prior studies suggest that lower-extremity arteries do not solely differ in terms of their anatomical position or diameter, but that hemodynamic turbulences, mechanical factors, endothelial dysfunction or histological differences as well as certain patient characteristics may help explain as to why patients develop clinical disease in the one artery, rather than in other arteries.[17, 45] For example, lesions in proximal arteries are often associated with younger female patients who are more likely to smoke, whereas diabetes is more prevalent in patients with lesions in distal arteries that is probably due to the presence of smooth muscle cells in the more distally located arteries that are affected by insulin.[17, 44, 45]

Prior findings suggest that not only the anatomical location but also the extensiveness of atherosclerosis (i.e., the number of arterial systems) is associated with patients' cardiovascular prognosis.[14, 16] Results from the REACH registry, for example, indicate that patients presenting with atherosclerosis in their coronaries, carotids, as well as their lower-extremities have a poorer cardiovascular prognosis as compared with those having a single system affected.[14, 16] Information on the extensiveness of *lower-extremity* arterial lesions is scarce since prior studies have limitedly focused on patients' adverse event risks by the presence of multiple vs. single lesions *within* one arterial system (e.g., lower-extremity arteries).[46] The exact etiological mechanisms at play have yet to be unraveled.

Figure 3. Anatomy of the lower-extremity arteries.



Adapted and modified from Norgren L. et al. EJVES 2007.[5] Re-used with permission of Elsevier©

1.3 Guideline recommended care

Lifelong treatment is indicated in PAD with a focus on relieving patients' symptoms, to improve their quality of life, limiting progression of their disease and reducing the risk of experiencing future adverse cardiovascular events.[4, 5, 12, 13] Present guidelines describe the various treatment strategies and provide some general recommendations as to when to refer patients for invasive versus non-invasive options.

Non-invasive treatment strategies

According to the current guidelines, treatment of symptomatic PAD (Fontaine 2) preferentially consists of non-invasive treatment options including cardiovascular risk management (e.g., dietary advices, smoking cessation, hypertension control, lipid lowering, and glycemic control in diabetics), optimal pharmacotherapy (statins and antiplatelet drugs) and supervised exercise therapy.[4, 5, 13, 47] It is recommended to maximize non-invasive treatment options first before proceeding with invasive strategies.

Invasive treatment strategies

Although patients with symptomatic PAD (Fontaine 2) are generally treated by non-invasive options only, invasive treatment strategies such as balloon angioplasty with or without stenting, endarterectomy, or bypass surgery can be considered in selected cases.[4, 5, 12] Endovascular options are generally used when favorable risk-benefit lesions are present in the aortoiliac arteries or in femoropopliteal arteries.[4, 5, 12] Surgical options such as endarterectomy and bypass surgery are indicated for aortoiliac lesions that are unsuitable for endovascular options or when patients' arterial anatomy is not sufficient for endovascular procedures. Although (cardiovascular) risks were found to be similar for endovascular and surgical procedures in critical limb ischemia patients within 2 years after diagnosis,[48, 49, 50] endovascular options are often preferred above surgical interventions because patients may more easily recover from endovascular strategies.[4, 5, 12]

It is recommended that invasive options should be reserved for patients who unsatisfactorily respond to non-invasive treatment, experience significant physical impairment or a reduced quality of life, who are at increased risk of disease progression and experiencing an adverse cardiovascular prognosis, or those who present with lesions that have a favorable risk-benefit ratio (aortoiliac disease) (Table 2 for overview of indications for invasive treatment referral by present guidelines). All indications listed in Table 2 are generally consistent across the ACC/AHA (American College of Cardiology/American Heart Association) Practice Guidelines, the TASC II (Trans-Atlantic Inter-Society Consensus) Consensus, as well as the Dutch guidelines (Dutch Societies of Surgery and Radiology) (Table 2).[4, 5, 13]

Performance measures

Although PAD guidelines have formulated general indications for invasive vs. non-invasive treatment referral, it is becoming increasingly clear that substantial variability exists in the quality of care that is delivered. For example, variations in the intensity of care have been documented in patients with PAD[51-53] (e.g., within the year before undergoing lower-extremity amputations).[53] The risk of experiencing cardiovascular events in PAD seems less well recognized as compared with coronary artery disease patients. This might be one of the major reasons why risk reduction strategies may not be consistently offered in patients with PAD.[54-56] These observations have led to the development of uniform performance measures (i.e., quantifying the appropriateness of clinical health care quality in a standardized manner)[57] for PAD to improve the quality of care in adults with PAD in outpatient settings.[56] For example, quantifying the quality of statin therapy to lower low-density cholesterol levels in patients with PAD is one of those defined performance measures.[56]

Table 2. Indications for invasive treatment referral according to the American, European and Dutch guidelines in patients with symptomatic lower-extremity PAD (Fontaine 2).

AHA guidelines	TASC II guidelines	Dutch guidelines
1. Predicted or observed lack of adequate response to exercise therapy and pharmacotherapy	1. Limitation that affects quality of life: - History of significant exercise limitation - Reduced treadmill performance - Reduced function by questionnaire	1. Impaired function status
2. Severe disability with the patient either being unable to perform normal work or having very serious impairment of other activities important to the patient	2. Symptoms that have not improved or deteriorated after claudication medical therapy or supervised exercise therapy	2. Insufficient benefits from non-invasive treatment options (e.g., risk factor modification, pharmacotherapy, exercise therapy)
3. Absence of other disease that would limit exercise even if the claudication was improved (e.g., angina or chronic respiratory disease)	3. Suspected proximal lesion	3. Anatomical location and morphology of the lesion
4. The anticipated natural history and prognosis of the patient		
5. The morphology of the lesions, which must be such that the appropriate intervention would have low risk and high probability of initial and long-term success		

Adapted from Hirsh A.T. et al. Circulation 2006; Norgren L. et al. EJVES 2007; Richtlijn diagnostiek en behandeling van arterieel vaatlijden van de onderste extremiteit 2005.[4, 5, 13] Abbreviations: AHA = American Heart Association, TASC = Trans-Atlantic Inter-Society Consensus.

1.4. The current thesis: Rationale and outline.

1.4.1. Background

Cardiovascular research has mainly focused on cardiac populations rather than patients with PAD. For example, cardiac research has focused on the identification of subpopulations, risk stratification initiatives as well as documenting the clinical decision-making process and patient-centered outcomes. However, these topics have received little attention in the field of PAD. The studies that have been performed in PAD are often based on the analogy with cardiac research. Given the medical and psychological burden of PAD, better documentation of outcomes of interest is clinically meaningful to both patients and their health care providers. The few studies that have been conducted in PAD have not yet been replicated, or include heterogeneous cohorts with small study populations.[17, 44] In addition, the identification of PAD subpopulations and risk stratification tools, as well as assessing patient-centered outcomes and evaluating the clinical decision-making process in PAD remains underexposed. These observations have led to the three overarching themes that will be addressed in this thesis. First, there will be a focus on identifying subpopulations in PAD with respect to arterial lesion characteristics, leg symptom presentation, health status, gender-related differences and depression. Second, the clinical-decision making process for invasive treatment referral in patients with PAD will be surveyed, and finally, (patient-centered) outcomes will be documented in greater detail for the identified subpopulations. Figure 1 provides an overview of the *Chapters* that will be addressed in this thesis.

1.4.2. Gaps in the current knowledge

Documenting subpopulations in PAD

Based on anatomic lesion location

Duplex ultrasound imaging for subsequent treatment for symptomatic PAD is guided by patients' clinical presentation and findings after physical examination. Prior research determined that proximal lesions are more often found in younger women who are current smokers, while distal lesions appear to be more present in older patients presenting with diabetes mellitus.[17, 44, 45]

It remains unclear whether a specific leg symptom profile (typical vs. atypical leg symptoms) is associated with having proximal or distal lesions in patients with PAD. *Chapter 2* documents the relationship between clinical presentation of symptomatic PAD – including patient characteristics, patients' self-reported leg symptoms as well as their cardiovascular risk profile – and anatomical lesion location within the lower extremities to identify PAD subgroups and to facilitate a differential, tailor-made treatment regimen for each specific subgroup.

Subpopulations based on pre-procedural health status

Patients' self-reported health status has been marginally evaluated in patients with PAD as compared with cardiac populations. Despite observations that PAD is associated with experiencing a poorer health status,[1-7, 10, 11] no studies have primarily focused on the identification of subpopulations by stratifying patients according to their pre-procedural health status. Therefore, little is known about which patients are at increased risk to report a lower health status. *Chapter 5* stratifies patients according to their pre-procedural physical health status scores to evaluate differences in patients' characteristics upon diagnosis.

Gender-related differences in peripheral arterial disease

Although patients might be stratified according to their anatomical lesion location or health status, prior observations also noted important gender-related differences.[58] Based on research in cardiac populations and preliminary findings in PAD, it is hypothesized that subpopulations can be identified by gender. *Chapter 6* therefore evaluates gender-related differences in characteristics of PAD patients.

Subpopulations in the depression burden of peripheral arterial disease

Patients with PAD not only experience significant medical comorbidities, but a substantial proportion of patients also experience a psychological burden.[1-7, 10, 11] Although depression has been commonly described in patients with PAD,[11, 59-61] it is under documented which patients are vulnerable to present with depressive symptoms and which patients are not. *Chapter 7* additionally stratifies patients according to their baseline depressive symptoms to determine what patient profile is associated with the presence of depressive symptoms in coexisting PAD.

The clinical decision-making process in PAD

Current guidelines suggest that several factors such as physical health status, anatomic lesion location, and cardiovascular risk factors should be taken into account in the clinical decision-making process to refer patients for invasive treatment.[4, 5, 13] Yet, it is unclear whether these factors are truly related to the decision-making process for invasive treatment referral in real-world clinical practice. *Chapter 3* provides novel insights in determinants for invasive treatment referral in daily clinical practice and explains how this knowledge may help to improve treatment strategies in the individual patient.

Outcomes in peripheral arterial disease

Multiple cardiovascular events

Given the identified subpopulations in PAD, it would be desirable to provide subpopulation-specific information on patients' risk of having an adverse prognosis. Specifically since PAD is associated with a substantially increased risk of adverse cardiovascular events and mortality. For example, patients with concomitant vascular disease in different arteries (i.e, PAD, CAD and/or CVD) are known to be at increased risk of experiencing adverse cardiovascular events or mortality as compared with patients having only one artery affected.[14, 16, 46] Yet, information on how the risk for adverse cardiovascular events (e.g., myocardial infarction, angina, stroke, transient ischemic attack and mortality) in patients with PAD differs by the extensiveness of *lower-extremity* lesions is lacking.

An older study with a limited sample size reported that patients with multiple arterial beds affected *within* the lower extremities have lower survival rates as compared with those having a single artery affected.[46] Recent studies determined that the number of femoral lesions improved prediction of cardiovascular death,[62] and that lesion composition differs by anatomical location.[63] Still, it remains unknown whether those with a greater disease burden (e.g., multiple vs. single lesions) would have an increased risk of experiencing a first as well as multiple cardiovascular events over time.

Chapter 4 evaluates patients' risks of experiencing first as well as multiple cardiovascular events by the extensiveness of *lower-extremity* arterial lesions using novel multiple event modeling techniques. Furthermore, it is addressed which type of event would mostly explain these adverse risks.

Health status benefits following invasive treatment

Although the primary goals of guideline recommended care for symptomatic PAD are to relieve patients' leg symptoms and to improve their quality of life,[4, 5, 13] the clinical-decision making process for invasive treatment referral in real-world clinical practice seems ambiguous. It is expected that the magnitude and pace of health status improvements are higher in patients that underwent invasive treatment. For example, six month results from the CLEVER trial indicate that patients' quality of life improved more in those undergoing stent revascularization as compared with supervised exercise treatment or optimal medical therapy.[64] Prior findings suggest, however, that health status benefits may vary among individuals undergoing invasive vs. non-invasive treatment due to other unknown factors.[3, 7] Because there is limited information available on health status benefits that can be expected by the receipt of invasive vs. non-invasive treatment, *Chapter 5* examines 1-year changes in patients' self-reported physical health status by invasive treatment referral.

The woman's position in cardiovascular outcomes and health status

Following patients' vulnerability of experiencing a significant lower health status and an adverse prognosis, prior research in the field of cardiology also indicated important gender-related disparities in health status and adverse prognosis. Women were more likely to report a lower health status or to be at increased risk of mortality and morbidity as compared with their male counterparts.[65-68] The American Heart Association recently launched a "Call to Action" to better document gender differences that may lead to the development of more gender-specific treatment strategies.[58] To date, however, documentation of gender disparities in association with patients' cardiovascular events and health status outcomes has been under exposed in PAD. *Chapter 6* prospectively documents novel information on gender differences in cardiovascular events and patients' self-reported health status outcomes following their PAD diagnosis.

Depressive symptoms following PAD diagnosis

As previously described, current guidelines mainly focus on medical aspects of lower-extremity PAD rather than patients' psychological vulnerabilities such as depression. Prior efforts demonstrated that approximately one fifth (16-36%) of the PAD population is affected by depression,[9, 11, 59-61, 69-71] and that younger women are specifically vulnerable for depressive symptoms.[61] Furthermore, patients with PAD and comorbid depression have increased risks of poorer outcomes (e.g., worse patency rates, cardiovascular events, and mortality) as compared with those without depression.[11, 69] Because evaluation of the psychological burden of PAD such as depression remains under addressed in the current medical literature, *Chapter 7* sought to explore determinants for depressive symptoms after 1-year follow-up as well as determinants for change in patients' self-reported depressive symptoms over time.

1.4.3. Addressing gaps in knowledge in peripheral arterial disease

The chapters in this thesis aim to provide novel insights in several identified gaps in the current scientific knowledge of lower-extremity peripheral arterial disease. *Chapter 8* summarizes and discusses the results from the separate chapters. A detailed overview of new insights that were generated with this thesis will be discussed to emphasize what this research adds to the current scientific and clinical knowledge base and how these new insights can help to advance the field of PAD.

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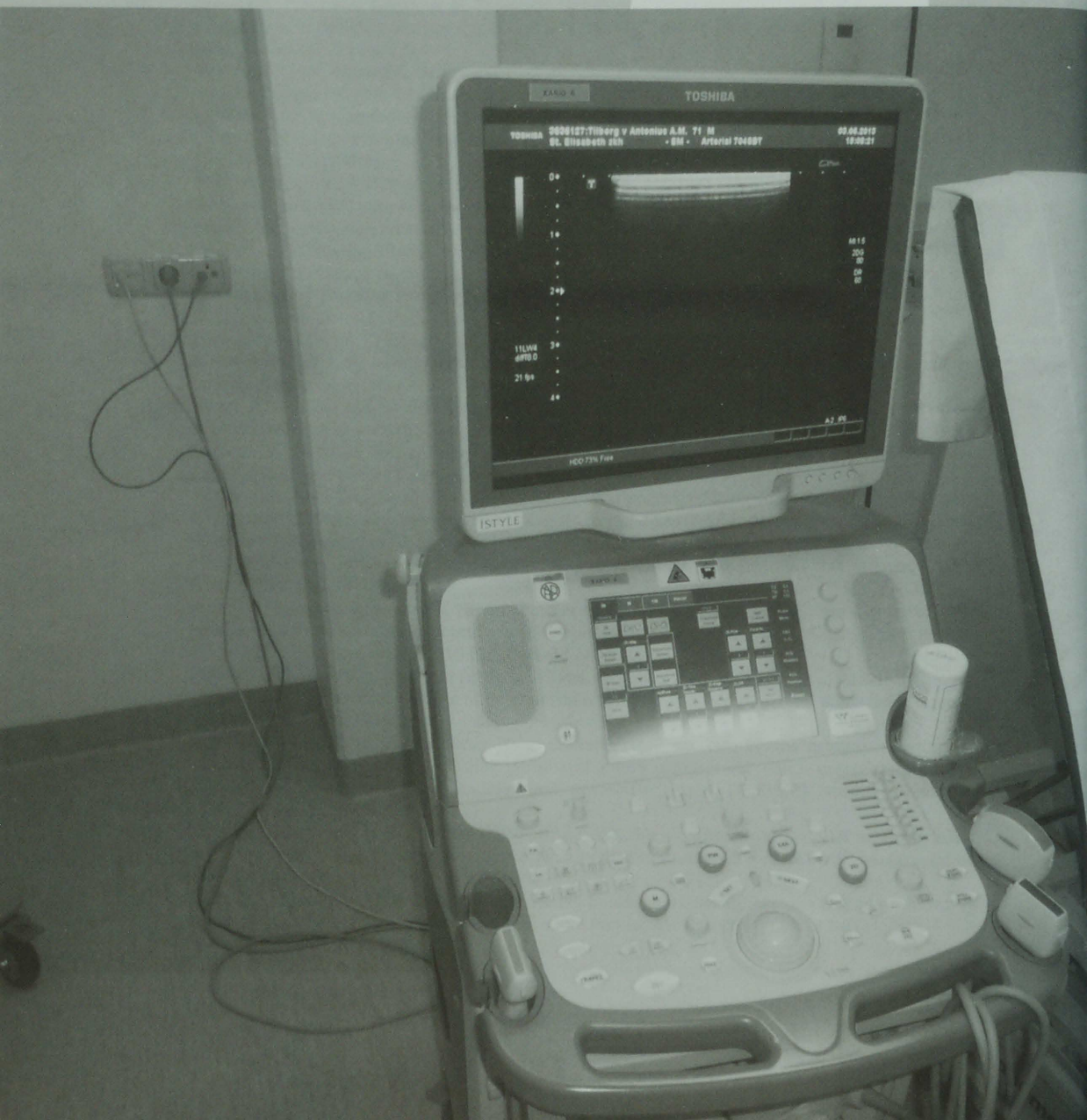
Chapter 2



Self-reported symptoms

on questionnaires and anatomic lesions on duplex ultrasound examinations in patients with peripheral arterial disease

2

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ABSTRACT

Objective: Whether a typical patient and symptom profile is associated with proximal or distal lesions in lower-extremity peripheral arterial disease (PAD) is unknown. Knowing which patient characteristics, exertional leg symptoms, and cardiovascular risk profile accompany the anatomic lesion location may facilitate a more tailor-made management of PAD.

Methods: This cross-sectional study comprised 701 patients from two vascular surgery outpatient clinics with new onset symptoms of PAD (Fontaine 2) who underwent duplex ultrasound (DUS) examinations from March 2006 to March 2011. The main outcome measures were patient characteristics, self-reported leg symptoms, and cardiovascular risk factors as documented from questionnaires and medical records. Peripheral lesion information, categorized by proximal and distal lesions, was obtained from DUS examinations. Multivariable logistic regression analyses were performed of proximal vs. non-proximal lesions, distal vs. non-distal lesions, and proximal and distal vs. absence of having both lesions to assess relationships between patient characteristics, leg symptom categories (typical vs. atypical leg symptoms), cardiovascular risk factors, and anatomic lesion location.

Results: Lesions were proximal in 270 (38.5%), distal in 441 (62.9%), and proximal and distal in 94 (13.4%). Patients with proximal lesions were younger (odds ratio [OR], 0.94, P<.0001) and less likely to be obese (OR=0.34, P<.0001) than those without proximal lesions. Older age (OR=1.07, P<.0001), male sex (OR=1.96, P=.003), being without a partner (OR=2.24, P=.004), and lower anxiety scores (OR=0.42, P=.003) were associated with distal lesions. Patients with both lesions were more likely to be single (OR=2.30, P=.010) and less likely to be obese (OR=0.24, P=.009).

No distinguishing leg symptom pattern was observed for patients with proximal lesions. Intermittent claudication was more frequently reported in those with distal lesions (P=.011). Although buttock and thigh pain seemed to be somewhat more present in proximal lesions (P<.01) and calf pain more in distal lesions (P<.001), patients still reported pain at a variety of levels throughout their legs, regardless of the anatomic lesion location.

Conclusions: Two distinctive PAD phenotypes – each with its own characteristics and risk factors – emerged by anatomic lesion location; however, PAD-specific leg symptoms did not always reflect the anatomic lesion location. These findings may open new opportunities to better tailor PAD management to these two PAD subgroups and may raise awareness about not relying on self-reported symptoms to guide further diagnostic imaging and peripheral lesion management.

INTRODUCTION

Peripheral arterial disease (PAD) of the lower-extremity arteries is a manifestation of generalized atherosclerosis and affects up to 3% to 10% of individuals, with prevalence rates up to 15% to 20% in those aged ≥ 70 years.[1-3] PAD affects arteries ranging proximally from the aortic bifurcation to the distally located foot arteries[4] and can be asymptomatic or present through exertional leg symptoms (typical or atypical).

Requests for diagnostic imaging and subsequent treatment for symptomatic PAD are typically guided by the clinical presentation of patients' symptoms and the information derived from the physical examination on a case-by-case basis. However, whether a typical patient and symptom profile can be assigned to groups of patients that have been diagnosed with proximal lesions, distal lesions, or patients with more diffuse lesions in both proximal and distal locations is unknown. Preliminary findings show that younger age and smoking are related to proximal PAD, whereas diabetes mellitus often appears in distal PAD.[4,5] These prior studies, however, were unable to study detailed information about patient characteristics and the relationship between self-reported leg symptom presentation and anatomic lesion location. Knowing which patient, symptom, and clinical profile may accompany certain lesion locations in PAD may allow us to distill distinct subpopulations that may potentially benefit from a more tailor-made treatment regimen.

Therefore, this study aimed to evaluate the association between the clinical presentation of symptomatic PAD – including patient characteristics, patients' self-reported exertional leg symptoms, and their cardiovascular risk profile – and anatomic lesion location.

METHODS

The study was approved by the Institutional Review Boards of the participating hospitals, and written informed consent was obtained from all participants.

Patients and study design

This study is a subsample of 701 individuals enrolled between March 2006 and March 2011 in an ongoing, prospective registry that consecutively enrolls patients presenting with newly diagnosed symptoms of PAD (Fontaine 2) from two vascular surgery outpatient clinics of the St. Elisabeth Hospital and the TweeSteden Hospital in Tilburg, the Netherlands. Patients enrolled in this database were eligible for inclusion if they had an abnormal resting ankle-brachial index (ABI) of ≤0.90 or a post-exercise ABI decrease of 15% after treadmill exercise test. The study excluded patients who had a non-compressible ABI (≥1.30), presented with critical limb ischemia, significant cognitive impairment, or severe psychiatric or somatic comorbidities (e.g., psychosis or active cancer treatment), or those with insufficient knowledge of the Dutch language. Because the current study focused on the location of lower-extremity arterial lesions, patients were additionally excluded if no baseline duplex ultrasound (DUS) examination was retrieved in their medical records ≤3 months after inclusion or if they previously underwent lower-extremity bypass surgery, because categorizations of arterial lesions according to the predefined segments on the DUS examinations were not feasible in this latter category (Figure 1).

All participating patients were clinically evaluated by vascular surgeons according to the institutional protocol and received a vascular diagnostic work-up, including measurement of the resting and post-exercise ABI in both legs, and a DUS examination to document peripheral arterial lesion characteristics (Figure 2). Patients also completed self-report questionnaires at their first visit when their PAD was evaluated by a vascular surgeon to document their demographic, socioeconomic, psychologic factors, and leg symptoms. Information on cardiovascular history, clinical factors, and medication use was obtained through medical record abstraction upon inclusion.

Vascular laboratory assessment

Trained vascular technicians measured the resting and post-exercise ABI to verify PAD diagnosis, using a handheld Doppler instrument (Imexlab 9000; Imex Medical Systems Inc, Golden Colorado). The ABI is considered to be abnormal and indicative of PAD if the resting ABI $\leq$0.90 or if the post-exercise ABI drops by 15% compared with the resting ABI.[6] Pain-free walking distance (PFWD) and maximum walking distance (MWD) were derived from a distance-limited (1000 meters) treadmill exercise protocol.

Figure 1 – Overview of the study population.

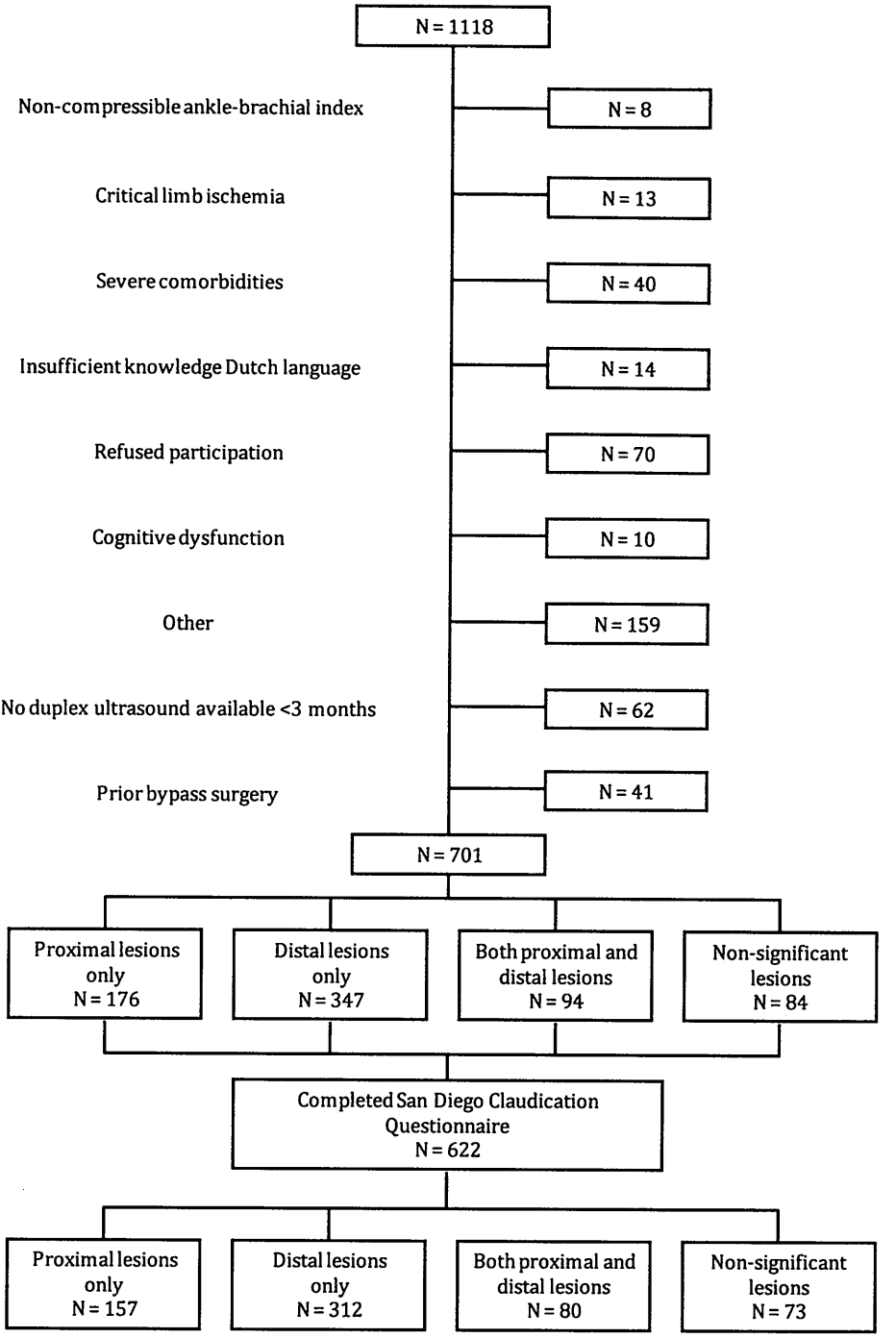
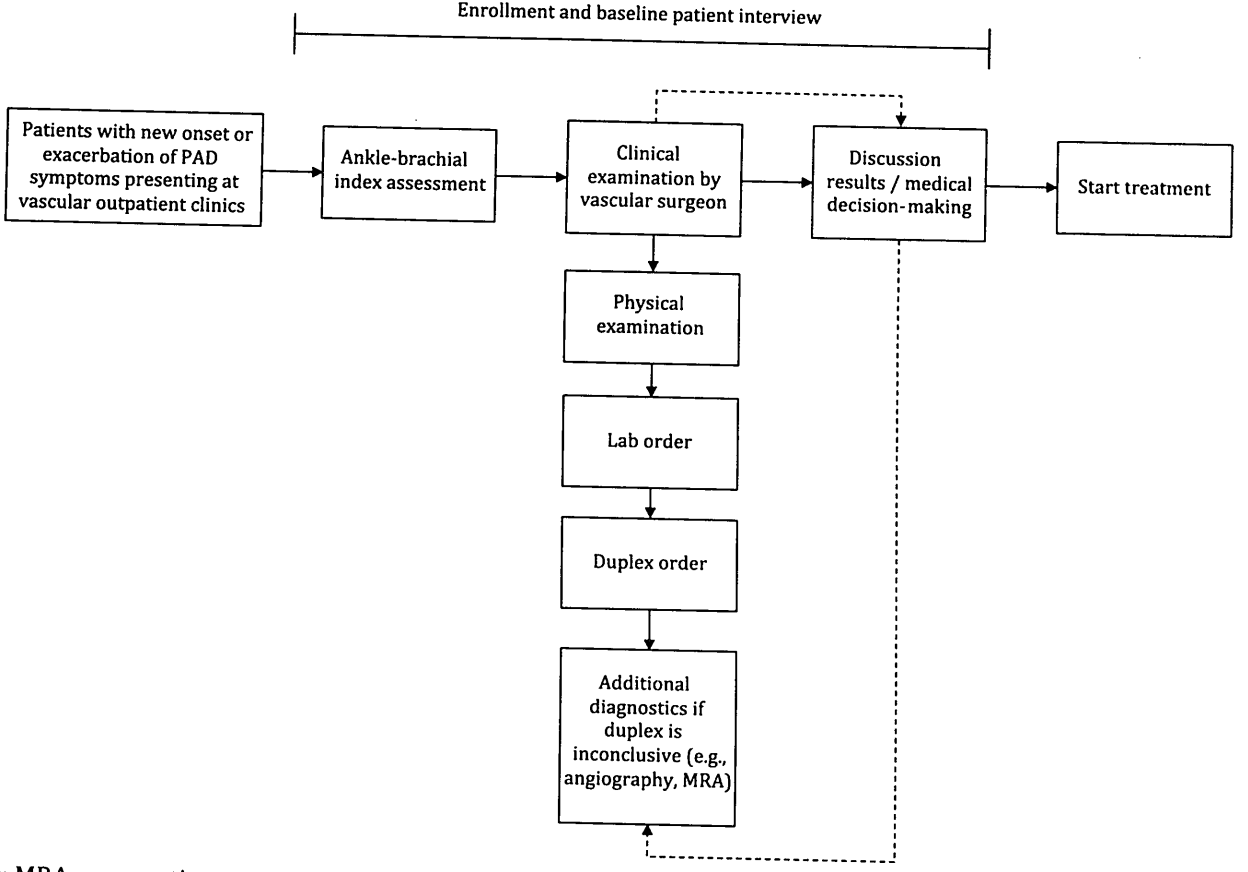


Figure 2 – Study design and overview of vascular diagnostic work-up process.



Abbreviations: MRA = magnetic resonance angiography; PAD = Peripheral arterial disease.

DUS protocol and lesion locations

DUS examinations were guided by the clinical examination of vascular surgeons and were performed by trained technicians to examine the exact location, extensiveness, and severity of lesions. A detailed description of the DUS imaging protocol is available in Appendix 1. The location of PAD lesions was derived from DUS readings by a team of three physicians (1 surgical fellow and 2 vascular surgeons). PAD lesions were categorized by location as: 1. proximal lesions – aortoiliac segments, including the distal abdominal aorta, right and left common iliac artery, right and left external iliac artery, and bifurcation of the right and left internal iliac artery; 2. distal lesions – femoropopliteal segments, including the right and left common femoral artery, bifurcation of the right and left deep femoral artery, the right and left superficial femoral artery, and right and left popliteal artery; and crural segments, including the right and left posterior tibial artery, right and left peroneal artery, and right and left anterior tibial artery; and 3. proximal and distal lesions – including lesions or occlusions that presented at both proximal and distal locations.

Because these three categories were not mutually exclusive, each lesion location category was compared against all patients who were not in that category (proximal vs. non-proximal, distal vs. non-distal, and both proximal and distal vs. absence of having both lesions). Lesions were considered significant if (1) a peak systolic velocity (PSV) ratio of $\geq$2.5 was measured, or if (2) an occlusion was observed (no flow, and no PSV ratio). In patients with lower-extremity PAD, color and pulsed-wave Doppler methodology used in DUS examinations has a sensitivity of 87% to 88% and a specificity of 95% to 99% to detect significant arterial lesions.[7]

Leg symptom groups

The San Diego Claudication Questionnaire was used to assess leg symptoms upon inclusion.[8,9] This standardized measure uses the Rose Claudication definition to determine leg-specific claudication and has a 91% sensitivity and 68% specificity for a clinician-based diagnosis of claudication.[10]

The self-reported symptoms were categorized into the following leg symptom categories: 1. typical exertional leg symptoms (or intermittent claudication), characterized by lower-extremity pain, discomfort, fatigue, or weakness in the buttock, thigh, or calf muscles that never begin at rest and are consistently produced by the same amount of walking or equivalent muscular activity, causing the patient to stop the activity, upon which symptoms are relieved <10 minutes; 2. atypical exertional leg symptoms, characterized by pain, numbness or discomfort, that do not begin at rest and do not cause the patient to stop the activity, or exertional leg symptoms that cause the patient to stop the activity, but do not involve the calves and do not resolve <10 minutes of rest; 3. symptoms at rest, defined as leg symptoms (pain, numbness, or discomfort) that patients experience while at rest, not to be confused with ischemic rest pain; and 4. no exertional leg symptoms, defined as the absence of exertional leg pain, numbness or discomfort or the absence of leg symptoms experienced at rest.[9,11,12]

For descriptive purposes only, the four different leg categories will be reported; for our main analyses, leg categories were additionally dichotomized by collapsing categories 2, 3, and 4 to represent the "atypical symptom presentation" vs. leg category 1 that represents "typical symptom presentation." We also used individual items on the San Diego Claudication Questionnaire to discern between the location of symptoms, including pain at the level of the buttocks, thighs, or calves.

Cardiovascular history, clinical factors, and medication use

Baseline patient information on cardiovascular history, clinical factors, and medication use was abstracted from medical records. Cardiovascular history included cardiac history (angina, myocardial infarction, coronary artery bypass surgery [CABG], percutaneous coronary intervention [PCI], and congestive heart failure) and cerebrovascular history (stroke, and transient ischemic attack [TIA]). Clinical factors included smoking status, diabetes mellitus, hyperlipidemia, hypertension, body mass index (BMI, kg/m^2), chronic obstructive pulmonary disease (COPD), renal dysfunction, chronic back pain, and knee or hip osteoarthritis.

Current medication use was categorized according to the following categories: aspirin, statins, beta blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, nitroglycerin, anticoagulants, digoxin, antiarrhythmics, antidepressants, anxiolytics, and hypnotics.

Other patient characteristics

Participants completed self-report questionnaires at baseline to provide information on demographic, socioeconomic, and psychologic factors. Demographic factors included age and sex. Socioeconomic factors consisted of marital status (partner vs. no partner), educational level (high school education or more vs. less than high school education), and working status (active vs. non active). Psychologic factors included distressed (Type D) personality, depression, and anxiety. Type D personality is defined as a joint tendency toward negative affectivity and social inhibition and was assessed by the Type D Scale-14 (DS14).[13] Consistent with prior work, a score $\geq$10 for the negativity and social inhibition subscales was used as a criterion to identify patients with a Type D personality.[13] Depression and anxiety were assessed using the 14-item self-report Hospital Anxiety and Depression Scale (HADS).[14] Cutoff scores of $\geq$8 for both subscales denoted clinically relevant symptoms of anxiety and depression.[14]

Statistical analysis

Patient characteristics, cardiovascular history, clinical factors by lesion location

Baseline characteristics were examined for the total sample and stratified by the presence of a proximal lesion, the presence of a distal lesion, and again stratified by the presence of having both a proximal and distal lesion. The Chi-square test was used to examine categorical variables and the Student's t-test for continuous variables that were normally distributed. For continuous variables that did not follow a normal distribution, the non-parametric Wilcoxon test was used.

Leg symptoms by lesion location

Self-report leg symptoms as assessed by the San Diego Claudication questionnaire and by breakdown of the four leg categories were similarly examined by the presence of a proximal lesion, the presence of a distal lesion, and by having both a proximal and distal lesion, discriminating between the leg symptom categories: (1) intermittent claudication vs. other, (2) atypical exertional leg symptoms vs. other, (3) symptoms at rest vs. other, and (4) no exertional leg symptoms vs. other. Likewise, the relationship among the locations of self-reported leg symptoms (buttock vs. not buttock, thigh vs. not thigh, and calf vs. not calf) was evaluated by lesion location. The Chi-square test was used for all comparisons.

Multivariable logistic regression analyses

Three sets of multivariable logistic regression analyses were conducted (enter method) to assess the relationship between a priori selected patient characteristics, leg symptom categories, and cardiovascular risk factors and anatomic lesion location: (1) proximal vs. non-proximal lesions, (2) distal vs. non-distal lesions, and (3) both proximal and distal vs. the absence of having both lesions.

Variables in all models included patient characteristics (age, sex, marital status, educational level), clinical factors (smoking status, hypertension, diabetes, renal dysfunction, BMI), cardiovascular history (cardiac history and cerebrovascular history), presenting leg symptom (typical leg symptom categories [symptom category 1] vs. atypical leg symptoms [symptom categories 2, 3, and 4]), and psychologic factors (depression, anxiety, and a distressed personality).

Sensitivity analyses

A set of sensitivity analyses was performed for leg symptoms by lesion location by excluding those patients who presented with both proximal and distal lesions. Analyses were replicated for the leg symptoms comparisons by proximal and distal lesions and for our main analyses, including the two multivariable logistic regression analyses ([1] proximal vs. non-proximal lesions, [2] distal vs. non-distal lesions). The same independent variables that were used in the main analyses were included in the replicated models. All analyses were performed using SPSS 17.0 software (SPSS Inc, Chicago, Ill) using 2-tailed tests, and values of $P<.05$ were considered statistically significant.

RESULTS

Patient characteristics, cardiovascular history, clinical factors by lesion location

A total of 701 DUS readings were obtained. A breakdown of segments imaged is listed in Table 1. Femoropopliteal segments were most commonly visualized, followed by aortoiliac segments and a minority of crural segments. Partial technical reading problems occurred in 73 DUS scans. For those images, we could confirm the lesion location from additional diagnostic tests (e.g., magnetic resonance angiography, angiography or additional abdominal ultrasound imaging) in 27 patients. If additional testing was not available, we relied on the physical examination (pulsations) or additional Doppler waveform analyses in the remaining patients.

At initial presentation at the outpatient clinic, 270 of 701 patients (38.5%) had proximal lesions, 441 (62.9%) had distal lesions, and 94 (13.4%) had proximal and distal lesions. The mean age of the cohort was 64.8 years, and 63.9% were men. Table 2 reports the baseline characteristics of the total sample (n=701), and stratified by proximal lesions, distal lesions, and both proximal and distal lesions. Patients with proximal lesions were significantly younger, had an active working status, and were less likely to have a history of angina, CABG, TIA, diabetes, and hypertension (Table 2). They were more likely to be smokers and more often experienced hip or knee pain. Their BMI was lower, and they were less likely to use cardiovascular medication (beta blockers, diuretics, ACE inhibitors, calcium antagonists, and antiarrhythmics), but were more likely to use aspirin. Patients with proximal lesions had a shorter PFWD and a lower resting, and post-exercise ABI than those without proximal lesions. Patients with distal lesions were older, more often male and without a partner, and less likely to have an active working status than those without distal lesions (Table 2). They were more likely to present with a history of CABG, diabetes, and hypertension, were less likely to be active smokers or to report back, hip or knee pain, and were more likely to be taking cardiovascular medications (beta blockers, diuretics, calcium antagonists, nitroglycerin, and antiarrhythmics). The resting and post-exercise ABI in patients with distal lesions was lower compared with those without distal lesions; and finally, patients with distal lesions felt less burdened by symptoms of anxiety.

Patients with both proximal and distal lesions were more likely to be without a partner, have an active working status, a history of myocardial infarction, and were being prescribed nitroglycerin. Patients with lesions in both locations also had a lower BMI, and a worse disease status, as attested by their shorter MWD and lower resting and post-exercise ABI values (Table 2).

Table 1 – Duplex ultrasound imaging information.

Variable	**No. (%) (n=701)**
Segment visualized	
Aortoiliac*	
Bilateral, n (%)	468 (66.8)
Unilateral, n (%)	47 (6.7)
Femoropopliteal*	
Bilateral, n (%)	320 (45.6)
Unilateral, n (%)	332 (47.4)
Crural segments*	
Bilateral, n (%)	32 (4.6)
Unilateral, n (%)	39 (5.6)
Stenoses (PSV ratio ≥ 2.5)	720
Occlusions, n (%)	521

PSV = Peak systolic velocity. *The common femoral artery was identified if only the aortoiliac segments were visualized or if only the femoropopliteal segments were visualized, because both examinations started at the groin(s).

Table 2 - Baseline characteristics of the total sample and stratified by lesion location.

	Total sample	Proximal lesions*			Distal lesions*			Both Proximal and Distal lesions*		
	(n=701)	Yes (n=270)	No (n=431)	P-value	Yes (n=441)	No (n=260)	P-value	Yes (n=94)	No (n=607)	P-value
Demographics										
Age, mean (range) years	64.8±10.0 (37-92)	**61.3±10.0**	**66.9±9.3**	**<.0001**	**67.4±9.2**	**60.4±9.7**	**<.0001**	66.1±9.6	64.6±10.0	.16
Male sex, n (%)	448 (63.9)	163 (60.4)	285 (66.1)	.12	**303 (68.7)**	**145 (55.8)**	**.001**	68 (72.3)	380 (62.6)	.07
Socioeconomic factors										
No partner, n (%)	139 (24.7)	51 (24.5)	88 (24.8)	.94	**105 (29.3)**	**34 (16.6)**	**.001**	**27 (38.0)**	**112 (22.8)**	**.005**
<High school education, n (%)	142 (25.4)	51 (25.0)	91 (25.6)	.86	94 (26.3)	48 (23.8)	.50	23 (32.9)	119 (24.3)	.13
Working full or part time, n (%)	147 (27.0)	**72 (36.0)**	**75 (21.8)**	**<.0001**	**76 (22.0)**	**71 (35.9)**	**<.0001**	**11 (16.4)**	**136 (28.5)**	**.037**
Cardiovascular history										
Angina pectoris, n (%)	108 (15.4)	**32 (11.9)**	**76 (17.6)**	**.039**	**76 (17.2)**	**32 (12.3)**	**.08**	20 (21.3)	88 (14.5)	.09
Myocardial infarction, n (%)	129 (18.4)	47 (17.4)	82 (19.0)	.59	89 (20.2)	40 (15.4)	.11	**25 (26.6)**	**104 (17.1)**	**.028**
CABG, n (%)	78 (11.1)	**21 (7.8)**	**57 (13.2)**	**.026**	**60 (13.6)**	**18 (6.9)**	**.007**	14 (14.9)	64 (10.5)	.21
PCI, n (%)	64 (9.1)	20 (7.4)	44 (10.2)	.21	41 (9.3)	23 (8.8)	.84	9 (9.6)	55 (9.1)	.87
Congestive heart failure, n (%)	35 (5.0)	8 (3.0)	27 (6.3)	.05	27 (6.1)	8 (3.1)	.07	4 (4.3)	31 (5.1)	.72
Stroke, n (%)	55 (7.8)	17 (6.3)	38 (8.8)	.23	39 (8.8)	16 (6.2)	.20	9 (9.6)	46 (7.6)	.50
TIA, n (%)	60 (8.6)	**12 (4.4)**	**48 (11.1)**	**.002**	43 (9.8)	17 (6.5)	.14	10 (10.6)	50 (8.2)	.44
Clinical factors										
Smoking, n (%)	352 (50.2)	**171 (63.3)**	**181 (42.0)**	**<.0001**	**198 (44.9)**	**154 (59.2)**	**<.0001**	54 (57.4)	298 (49.1)	.13
Diabetes mellitus, n (%)	172 (24.5)	**41 (15.2)**	**131 (30.4)**	**<.0001**	**125 (28.3)**	**47 (18.1)**	**.002**	17 (18.1)	155 (25.5)	.12
Hypercholesterolemia, n (%)	483 (68.9)	185 (68.5)	298 (69.1)	.86	308 (69.8)	175 (67.3)	.48	72 (76.6)	411 (67.7)	.08
Hypertension, n (%)	417 (59.5)	**144 (53.3)**	**273 (63.3)**	**.009**	**281 (63.7)**	**136 (52.3)**	**.003**	59 (62.8)	358 (59.0)	.49
BMI (kg/m^2), mean	26.7±4.9	**25.3±3.5**	**27.5±5.4**	**<.0001**	26.9±4.6	26.4±5.3	.25	**25.4±3.0**	**26.9±5.1**	**.015**
COPD, n (%)	117 (16.7)	40 (14.8)	77 (17.9)	.29	67 (15.2)	50 (19.2)	.17	11 (11.7)	106 (17.5)	.16
Renal dysfunction, n (%)	59 (8.4)	17 (6.3)	42 (9.7)	.11	42 (9.5)	17 (6.5)	.17	7 (7.4)	52 (8.6)	.72

	Total sample (n=701)	Proximal lesions*			Distal lesions*			Both Proximal and Distal lesions*		
		Yes (n=270)	No (n=431)	P-value	Yes (n=441)	No (n=260)	P-value	Yes (n=94)	No (n=607)	P-value
Table 2 (Continued)										
Back pain, n (%)	81 (13.7)	38 (16.7)	43 (11.8)	.09	**43 (11.5)**	**38 (17.4)**	**.041**	10 (12.3)	71 (13.9)	.71
Hip or knee pain, n (%)	121 (20.4)	**57 (25.0)**	**64 (17.6)**	**.029**	**64 (17.1)**	**57 (26.1)**	**.009**	14 (17.3)	107 (20.9)	.45
Medication use										
Aspirin, n (%)	546 (77.9)	**221 (81.9)**	**325 (75.4)**	**.045**	336 (76.2)	210 (80.8)	.16	77 (81.9)	469 (77.3)	.31
Statins, n (%)	572 (81.6)	224 (83.0)	348 (80.7)	.46	354 (80.3)	218 (83.8)	.24	81 (86.2)	491 (80.9)	.22
β-blocker, n (%)	296 (42.2)	**96 (35.6)**	**200 (46.4)**	**.005**	**202 (45.8)**	**94 (36.2)**	**.012**	42 (44.7)	254 (41.8)	.60
Diuretics, n (%)	168 (24.0)	**46 (17.0)**	**122 (28.3)**	**.001**	**132 (29.9)**	**36 (13.8)**	**<.0001**	28 (29.8)	140 (23.1)	.16
ACE inhibitor, n (%)	223 (31.8)	**73 (27.0)**	**150 (34.8)**	**.032**	151 (34.2)	72 (27.7)	.07	34 (36.2)	189 (31.1)	.33
Calcium antagonist, n (%)	157 (22.4)	**45 (16.7)**	**112 (26.0)**	**.004**	**113 (25.6)**	**44 (16.9)**	**.008**	23 (24.5)	134 (22.1)	.61
Nitroglycerin, n (%)	62 (8.8)	23 (8.5)	39 (9.0)	.81	**47 (10.7)**	**15 (5.8)**	**.028**	**18 (19.1)**	**44 (7.2)**	**<.0001**
Anticoagulants, n (%)	114 (16.3)	38 (14.1)	76 (17.6)	.21	78 (17.7)	36 (13.8)	.18	21 (22.3)	93 (15.3)	.09
Digoxin, n (%)	18 (2.6)	6 (2.2)	12 (2.8)	.65	14 (3.2)	4 (1.5)	.19	4 (4.3)	14 (2.3)	.27
Antiarrhythmics, n (%)	19 (2.7)	**3 (1.1)**	**16 (3.7)**	**.039**	**17 (3.9)**	**2 (0.8)**	**.015**	2 (2.1)	17 (2.8)	.71
Antidepressives, n (%)	40 (5.7)	16 (6.0)	24 (5.6)	.83	22 (5.0)	18 (7.0)	.28	4 (4.3)	36 (6.0)	.51
Anxiolytics, n (%)	29 (4.1)	8 (3.0)	21 (4.9)	.22	15 (3.4)	14 (5.4)	.20	3 (3.2)	26 (4.3)	.62
Hypnotics, n (%)	33 (4.8)	12 (4.5)	21 (5.0)	.74	21 (4.9)	12 (4.7)	.88	4 (4.3)	29 (4.9)	.80
Vascular laboratory assessment										
PFWD, m	70.0±120.3	**70.0±104.7**	**80.0±128.8**	**.06**	80.0±126.4	70.0±109.4	.08	80.0±120.2	70±120.4	.88
MWD, m	250.0±312.4	250±302.5	260.0±318.4	.27	250.0±314.9	260.0±308.7	.60	**200.0±292.4**	**260.0±314.9**	**.039**
Ankle-brachial index										
Resting, %	65.9±16.8	**64.1±16.5**	**67.0±16.8**	**.027**	**62.2±15.5**	**72.1±17.0**	**<.0001**	**57.9±15.7**	**67.2±16.6**	**<.0001**
Post-exercise, %	36.0±19.3	**33.0±18.5**	**39.0±19.6**	**<.0001**	**32.0±18.0**	**43.0±20.0**	**<.0001**	**27.0±16.4**	**37.0±19.3**	**<.0001**

	Total sample (n=701)	Proximal lesions*			Distal lesions*			Both Proximal and Distal lesions*		
		Yes (n=270)	No (n=431)	P-value	Yes (n=441)	No (n=260)	P-value	Yes (n=94)	No (n=607)	P-value
Table 2 (Continued)										
Psychological factors										
Type D personality, n (%)	128 (23.1)	50 (24.3)	78 (22.3)	.60	75 (21.4)	53 (25.9)	.23	19 (27.5)	109 (22.4)	.35
Depression, n (%)	163 (29.3)	64 (30.9)	99 (28.3)	.51	101 (28.5)	62 (30.7)	.58	23 (32.4)	140 (28.8)	.54
Anxiety, n (%)	141 (25.3)	61 (29.5)	80 (22.9)	.08	**69 (19.4)**	**72 (35.6)**	**<.0001**	15 (21.1)	126 (25.9)	.39

Abbreviations: BMI = body mass index, CABG = coronary artery bypass surgery, COPD = chronic obstructive pulmonary disease, MWD = maximum walking distance, PCI = percutaneous coronary intervention, PFWD = pain-free walking distance, TIA = transient ischemic attack. *Numbers may not completely match across different comparison categories because non-mutually exclusive data are presented. Continuous data are presented as median±SD (or mean, as indicated) and range. Categoric data are presented as number (%). Bold indicates statistically significant results.

Leg symptoms by lesion location

The San Diego Claudication Questionnaire was completed for 622 patients. Typical exertional leg symptoms were reported in 43.6% of the total population, atypical exertional leg symptoms were present in 31.2%, symptoms at rest in 21.4%, and 3.9% reported being without exertional leg symptoms (Table 3). No distinguished leg symptom pattern emerged in patients presenting with proximal lesions, whereas patients with distal lesions and those with both proximal and distal lesions were the only ones who reported symptoms of intermittent claudication more frequently (P=.011 and P=.007, respectively; Table 3). Patients with proximal lesions more frequently reported having pain in their buttocks (P<.0001) or thighs (P=.004); patients with distal lesions more often had pain in their calfs (P<.0001). No differences in leg symptom presentation were observed in patients with proximal and distal lesions compared with those without lesions in both locations. Despite some statistically significant patterns, all levels of leg symptoms were well represented across anatomic categories.

Multivariable logistic regression analyses

Results of the three multivariable logistic regression models examining the association of patient characteristics, cardiovascular risk factors, and leg symptom categories with anatomic lesion location are presented in Figures 3, 4, and 5. Patients with proximal lesions were more likely to be younger (odds ratio [OR]=0.94, P<.0001) and have a lower BMI (OR=0.34, P<.0001) than those with non-proximal lesions (Figure 3). These factors were independent indicators of having proximal vs. non-proximal lesions.

Patients with distal lesions were more likely to be older (OR=1.07, P<.0001), male (OR=1.96, P=.003), without a partner (OR=2.24, P=.004), and less likely to be anxious (OR=0.42, P=.003) than those with non-distal lesions (Figure 4) in the full model, including demographic, socioeconomic factors, cardiac history, clinical factors, and leg symptoms. Patients with proximal and distal lesions were more likely to be without a partner (OR=2.30, P=.010) and to have a significantly lower BMI (OR=0.24, P=.009) than those without proximal and distal lesions after full model adjustment (Figure 5).

Sensitivity analyses

Full model results of all sensitivity analyses are presented in Appendices 2 and 3. Results for the leg symptom comparisons by lesion location, excluding those with both proximal and distal lesions, were similar than the original analyses for proximal vs. non-proximal lesions and distal vs. non-distal lesions (Appendix 2). When repeating the two multivariable logistic regression analyses (proximal vs. non-proximal lesions and distal vs. non-distal lesions), excluding those with lesions in both proximal and distal locations, we identified the same robust indicators of having proximal lesions (younger age, lower BMI), and for having distal lesions (older age, male sex, being without a partner, lower anxiety levels) compared with the indicators identified from our main analyses (Appendix 3).

Table 3 – Self-reported leg symptom category and location of the total sample, and stratified by lesion location.

Self-reported variable	Total sample (n = 622)	Proximal lesions*			Distal lesions*			Both Proximal and Distal lesions*		
		Yes (n=237)	No (n=385)	P-value	Yes (n=392)	No (n=230)	P-value	Yes (n=80)	No (n=542)	P-value
Leg symptom category										
Intermittent claudication, n (%)	271 (43.6)	103 (43.5)	168 (43.6)	.97	**186 (47.4)**	**85 (37.0)**	**.011**	**46 (57.5)**	**225 (41.5)**	**.007**
Atypical exertional leg symptoms, n (%)	194 (31.2)	75 (31.6)	119 (30.9)	.85	115 (29.3)	79 (34.3)	.19	18 (22.5)	176 (32.5)	.07
Symptoms at rest, n (%)	133 (21.4)	50 (21.1)	83 (21.6)	.86	75 (19.1)	58 (25.2)	.07	12 (15.0)	121 (22.3)	.14
No exertional leg symptoms, n (%)	24 (3.9)	9 (3.8)	15 (3.9)	.89	16 (4.1)	8 (3.5)	.71	4 (5.0)	20 (3.7)	.57
Leg symptom location										
Buttock, n (%)	238 (38.3)	**127 (53.6)**	**111 (28.8)**	**<.0001**	**111 (28.3)**	**127 (55.2)**	**<.0001**	31 (38.8)	207 (38.2)	.92
Thigh, n (%)	511 (82.2)	**208 (87.8)**	**303 (78.7)**	**.004**	314 (80.1)	197 (85.7)	.08	71 (88.8)	440 (81.2)	.10
Calf, n (%)	560 (90.0)	**198 (83.5)**	**362 (94.0)**	**<.0001**	**372 (94.9)**	**188 (81.7)**	**<.0001**	72 (90.0)	488 (90.0)	.92

*Numbers may not completely match across different comparison categories because non-mutually exclusive data are presented. Data are presented as number (%). Bold indicates statistically significant results.

Figure 3 - The relationship between patient characteristics, symptom presentation, and cardiovascular profile, and having proximal lesions. The risk estimates are shown as odds ratios (OR) and the corresponding 95% confidence intervals (CI).

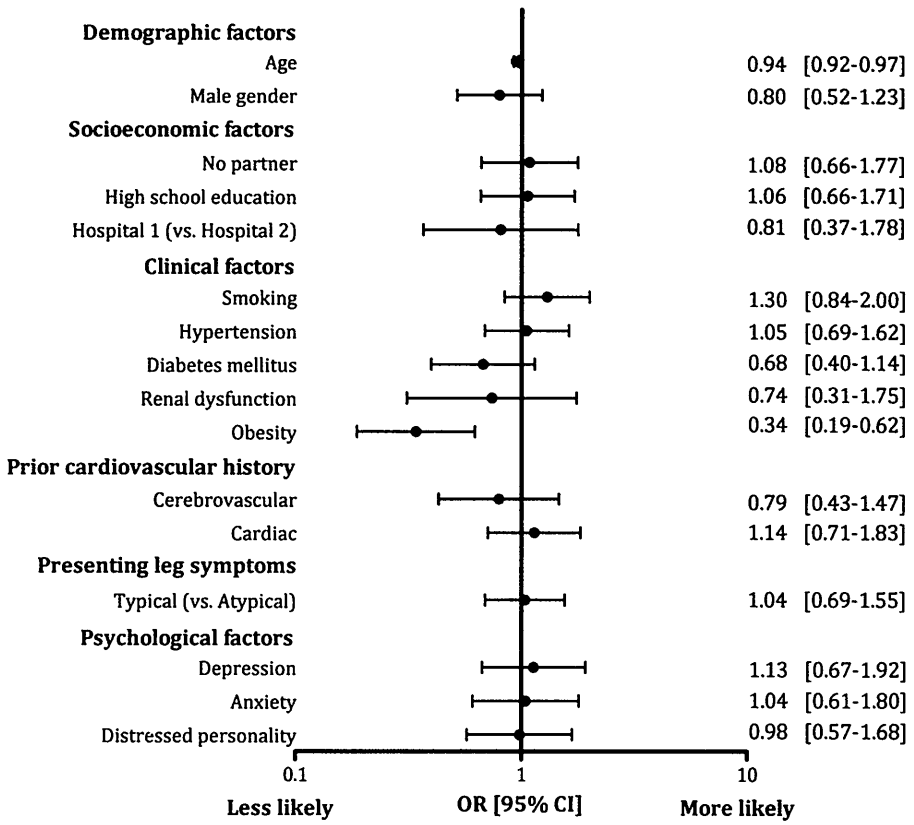


Figure 4 - The relationship between patient characteristics, symptom presentation, and cardiovascular profile, and having distal lesions. The risk estimates are shown as odds ratios (OR) and the corresponding 95% confidence intervals (CI).

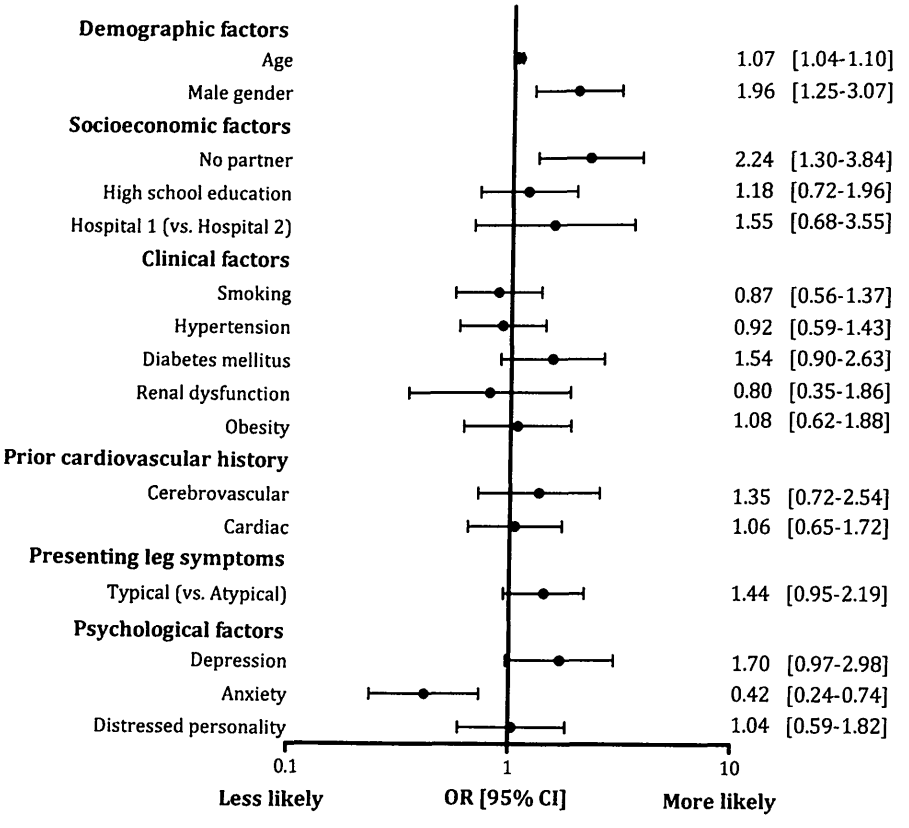
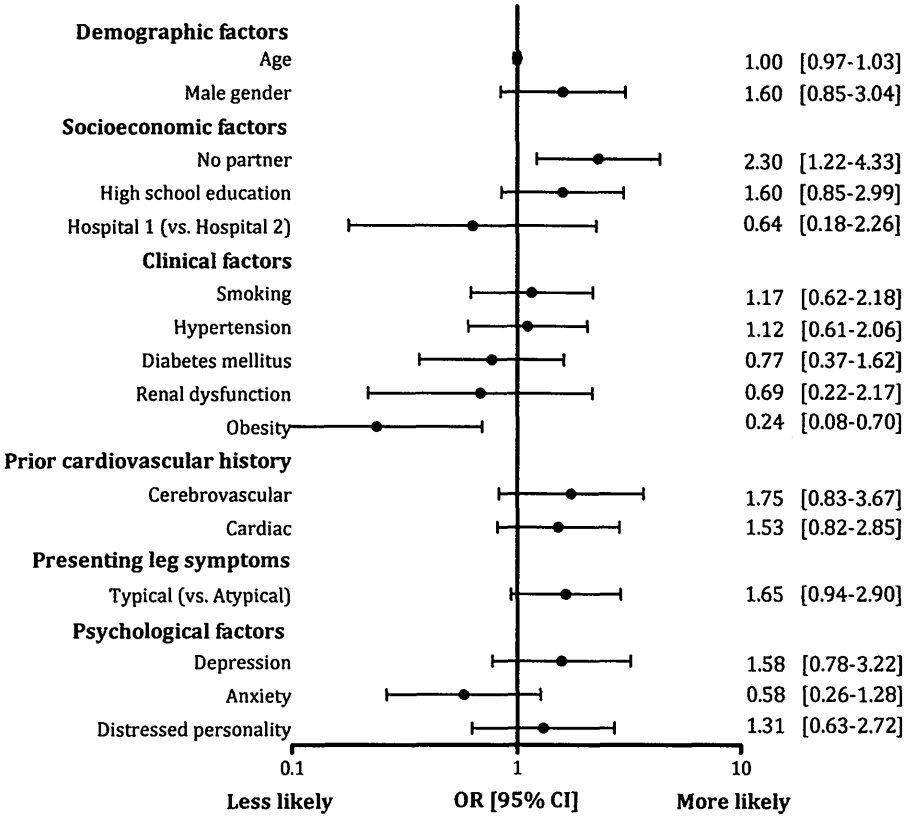


Figure 5 – The relationship between patient characteristics, symptom presentation, and cardiovascular profile, and having both proximal and distal lesions. The risk estimates are shown as odds ratios (OR) and the corresponding 95% confidence intervals (CI).



DISCUSSION

Most of the patients presenting with symptomatic disease at two vascular specialty clinics in the Netherlands appeared to have distal lesions, whereas more than one third presented with proximal lesions. When both groups of patients were systematically characterized by their anatomic lesion presentation, two distinct profiles emerged: the younger patient presenting without other comorbidities like obesity, who most likely had proximal lesions, vs. the older male patient with cardiovascular comorbidities who did not feel too much burdened by symptoms of anxiety accompanying his PAD, which most likely presented with distal lesions. No clear symptom pattern emerged by anatomic location, although classical symptoms of intermittent claudication were more present among patients with distal lesions. Buttock or thigh pain was more common in proximal lesions, but calf pain was more present among patients with distal lesions. Despite this statistically significant pattern, a variety of self-reported leg symptoms – including atypical vs. typical symptoms, as well as pain at the level of the buttocks, thighs, and calves – were well represented across both anatomic lesion categories, highlighting the discrepancy between what was defined as the relevant diseased segments in routine clinical practice and patients' self-reported symptom complex.

The current study addresses several gaps in knowledge and has the potential to advance the field in multiple ways: our study is a valuable replication of prior work in smaller populations that was unable to adjust for more granular information on socioeconomic, clinical, and psychosocial background, as our study did.[4,5,15] Having enrolled a more homogeneous population – newly diagnosed Fontaine 2 patients – rather than a mixed cohort, including patients with longer-existing disease and patients with critical limb ischemia,[4,5,15] also enhances the clinical interpretability of our results. In addition, to the best of our knowledge, this is the first study to provide novel insights in the relationship between the whole spectrum of self-reported leg symptoms and the anatomic lesion location derived from DUS imaging that was ordered by a vascular surgeon after a thorough history-taking and clinical examination at the vascular outpatient clinic.

The observation of having two distinct patient profiles that can be associated with different anatomic lesions may open up new opportunities to better accommodate PAD prevention and treatment strategies tailored to the individual patient and its risk factors. Although all patients in this study had Fontaine 2 PAD, and guideline-recommended treatment is warranted in all these patients; younger patients – often smokers – but not yet burdened by other cardiovascular and other comorbidities may additionally benefit from close monitoring, intensified secondary prevention, and educational and rehabilitation programs to prevent further disease progression and to minimize the risk of future cardiovascular events. This would especially be important when a patient undergoes an immediate revascularization procedure upon diagnosis and obtains a "quick relief" of symptoms, perhaps making patients not realize that the underlying atherosclerotic process is still present.

Our findings also generate the hypothesis that patients presenting with proximal lesions may have been exposed to a more aggressive type of atherosclerosis, hence the earlier age of presentation and a greater vulnerability for an adverse cardiovascular prognosis.[4] Patients with distal lesions, however, were older and seemed to be less anxious about their condition but presented with a challenging combination of multiple cardiovascular and other clinical risk factors that might require additional expertise and multidisciplinary management as well as extra assistance for the elderly patient who needs to be adherent to more medications and more treatment protocols to manage their multiple comorbidities. We conclude from these insights and hypotheses that future research is warranted on how different the pathophysiologic process of atherosclerosis underlying PAD may be in certain subgroups, as well as clinical research on the differential, more targeted management of subpopulations of patients and their impact on outcomes.

Our study also illustrated that relying on patients' self-reported symptoms to guide further diagnostic testing may seem to represent a real challenge because buttock, thigh, and calf pain were well represented in both proximal and distal lesions. Additionally, a clinician looking to see the classical presentation of intermittent claudication might only identify these in patients with distal lesions and might miss patients with proximal lesions because intermittent claudication was not particularly characteristic of this type of lesion. What this study describes is a widely variable symptom pattern among patients with symptomatic PAD, with only some patients presenting with classical intermittent claudication, which not only obscures the diagnosis of the disease among, for example, women,[11,16] but which may also not be so informative to help determine the location of the stenotic lesion. Studies evaluating how many significant lesions would be overlooked when only imaging part of the arterial segments and studies examining cost-effectiveness aspects of systematically imaging all segments vs. focused imaging based on the clinical presentation will be important directions for future research.

The two distinctive phenotypes observed in this study may not only have great face validity but may also be supported by the existence of potentially two different types of pathophysiologic mechanisms underlying these categories. Previous observations indicate several histologic and biochemical differences in large-vessel and small-vessel disease that might affect the development and restenosis rates after interventions of proximal vs. distal atherosclerosis within the lower extremities differently.[4,5,17-19] For example, smooth muscle cells in the distal arteries are more prone to be affected by insulin, which may illustrate the higher prevalence of diabetes in distal PAD.[17]

This study has several limitations that need to be considered when interpreting our results: First, the cross-sectional design does not allow us to infer causality, and residual confounding cannot be precluded. Second, our study may have underestimated the actual number of arterial lesions because DUS scans were guided by the clinical examination, including presenting leg symptoms, and because lesions might have been present in sequence, which potentially decreased the sensitivity to detect more downstream stenoses.[20] However, our study provides information reflecting real-world clinical practices with regards to the diagnostic work-up of PAD as organized in a vascular specialty clinic. Third, only two institutions were included in the present study, and findings may not be generalizable to other settings. Finally, we were not able to explicitly validate the spectrum or level of leg symptoms in PAD against anatomic lesion information, but instead, correlated patient characteristics, including self-reported leg symptoms, with lesion categories based on DUS information collected in routine clinical practice.

CONCLUSIONS

The observation of two distinct subpopulations based on patients' lower-extremity lesions, its associated patient characteristics, and the variability in symptom presentation associated with each of these lesions may raise questions about how we organize the diagnostic process for PAD and warrants further research that addresses opportunities to customize PAD management and prevention according to these subprofiles with the hopes to further optimize their outcomes.

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APPENDIX 1 - Duplex ultrasound protocol details

Duplex ultrasound (DUS) scans were performed by trained vascular technicians using the Toshiba Xario (Xario XG; Toshiba Medical Systems, Europe, Zoetermeer, the Netherlands). The superficial and abdominal aortoiliac arteries were visualized using an 8- to 9-MHz vascular probe and a 5-MHz convex transducer, respectively. A 4- to 7-MHz linear transducer was used for femoropopliteal and crural segments. B-mode, pulse repetition frequency, steer, and gain were tuned according to the examined segment. The color Doppler beam was held in a 60° angle to visualize the proximal, distal and middle part of each segment, and Doppler waveforms were used to assess flow.[1] The whole segment was carefully imaged in case flow disturbances were present. Possible stenoses were traced by increased velocities, spectral broadening, color disturbance, poststenotic waveforms, and diameter reduction.[1]

Examination of the aortoiliac segments started by imaging the common femoral artery at the groin, and segments were followed to the distal part of the abdominal aorta. The aortoiliac bifurcation was also transversally imaged to ensure that the entire segment was examined. A measuring-tape was placed on the upper leg, right above the patella, to consistently describe each lesion location in the femoropopliteal segments. The common femoral artery was identified first in transverse section, and all femoropopliteal segments were further followed by longitudinal imaging. The popliteal artery was transversally imaged in the middle of the popliteal fossa and longitudinally followed toward the crural segments.[2] The crural segments – including the anterior and posterior tibial artery as well as the peroneal artery – were longitudinally imaged, starting from the middle part of the popliteal fossa. Peak systolic velocities (PSV [cm/s]) were measured proximal to and at the site of the stenosis. PSV ratios were calculated to assess lesion severity (intrastenotic PSV divided by proximally measured PSV). Different transducer positions were used to visualize stenoses or occlusions if arteries were calcified. Because the detection of downstream stenoses by DUS imaging has a lower sensitivity of 60% to 65% when sequential lesions are present,[3] we additionally analyzed the morphology of Doppler waveforms to obtain information about the presence of lesions in a closer segment.

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APPENDIX 2 – Self-reported leg symptom category and location of the total sample, and stratified by lesion location (sensitivity analysis – without both proximal and distal lesions).

	Total sample	Proximal lesions*			Distal lesions*		
Self-reported category	(n =542)	Yes (n=157)	No (n=385)	P-value	Yes (n=312)	No (n=230)	P-value
Leg symptom category							
Intermittent claudication, n (%)	225 (41.5)	57 (36.3)	168 (43.6)	.12	140 (44.9)	85 (37.0)	.07
Atypical exertional leg symptoms, n (%)	176 (32.5)	57 (36.3)	119 (30.9)	.22	97 (31.1)	79 (34.3)	.42
Symptoms at rest, n (%)	121 (22.3)	38 (24.2)	83 (21.6)	.50	63 (20.2)	58 (25.2)	.17
No exertional leg symptoms, n (%)	20 (3.7)	5 (3.2)	15 (3.9)	.69	12 (3.8)	8 (3.5)	.82
Leg symptom location							
Buttock, n (%)	207 (38.2)	**96 (61.1)**	**111 (28.8)**	**<.0001**	**80 (25.6)**	**127 (55.2)**	**<.0001**
Thigh, n (%)	440 (81.2)	**137 (87.3)**	**303 (78.7)**	**.021**	**243 (77.9)**	**197 (85.7)**	**.022**
Calf, n (%)	488 (90.0)	**126 (80.3)**	**362 (94.0)**	**<.0001**	**300 (96.2)**	**188 (81.7)**	**<.0001**

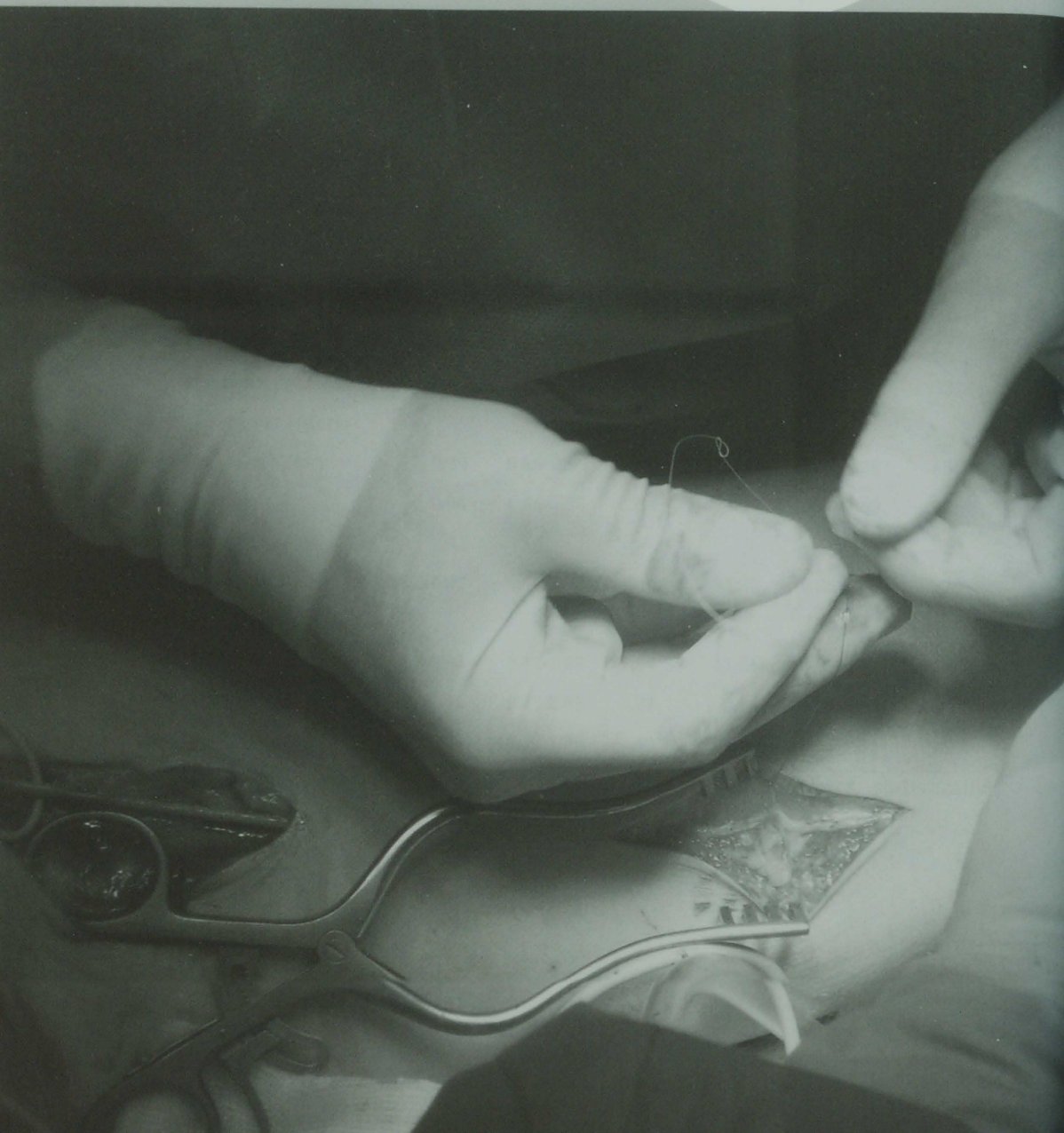
*Numbers may not completely match across different comparison categories because non-mutual exclusive data are presented. Data are shown as number (%). Bold indicates statistically significant results.

APPENDIX 3 - The relationship between a priori selected patient characteristics, cardiovascular risk factors and leg symptom presentation and lesion location (sensitivity analysis - without both proximal and distal lesions).

	Proximal lesions			Distal lesions		
Variable	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Demographic factors						
Age	**0.92**	**0.89-0.95**	**<.0001**	**1.08**	**1.05-1.11**	**<.0001**
Male sex	**0.58**	**0.35-0.97**	**.040**	**1.97**	**1.22-3.18**	**.006**
Socioeconomic factors						
No partner	0.68	0.35-1.28	.23	**1.92**	**1.08-3.42**	**.028**
Less than high school education	0.82	0.44-1.53	.53	1.01	0.59-1.73	.97
Hospital	0.93	0.37-2.36	.88	1.76	0.75-4.13	.19
Clinical factors						
Smoking	1.35	0.80-2.28	.26	0.86	0.53-1.37	.52
Hypertension	1.00	0.60-1.66	.99	0.88	0.55-1.41	.59
Diabetes mellitus	0.75	0.39-1.46	.40	1.61	0.92-2.81	.09
Renal dysfunction	0.83	0.26-2.68	.76	0.83	0.34-1.98	.67
Body mass index	**0.42**	**0.21-0.86**	**.017**	1.33	0.76-2.36	.32
Prior cardiovascular history						
Cerebrovascular history	**0.39**	**0.15-0.99**	**.048**	1.17	0.60-2.28	.65
Cardiac history	0.84	0.46-1.53	.56	1.01	0.60-1.69	.98
Presenting leg symptoms						
Typical (vs. atypical)	0.81	0.49-1.33	.40	1.32	0.85-2.06	.22
Psychological factors						
Depression	0.93	0.47-1.85	.84	1.51	0.83-2.77	.18
Anxiety	1.46	0.75-2.85	.27	**0.44**	**0.24-0.82**	**.009**
Distressed personality	0.78	0.40-1.55	.48	0.98	0.53-1.81	.96

Abbreviations: CI=confidence interval, OR=odds ratio. Bold indicates statistically significant results.

Chapter 3



Determinants of invasive treatment

in lower-extremity peripheral arterial disease

in a real-world clinical setting

3

M. van Zitteren, P.W. Vriens, D.H. Burger, W.M. de Fijter, G.P. Gerritsen, J.M. Heyligers, M.J. Nooren, J. Denollet, K.G. Smolderen. Determinants of invasive treatment in lower-extremity peripheral arterial disease: insights from a real-world clinical setting. *Submitted.*

ABSTRACT

Objective: Since it is unknown what factors are weighed in a clinician's decision to refer patients with symptomatic lower-extremity peripheral arterial disease (PAD) for invasive treatment, we examined the relationship between health status, lesion location, and site variations and invasive treatment referral ≤1 year following diagnosis in patients with PAD seen in a real-world clinical setting.

Design of study: Prospective observational cohort study.

Setting: Ambulatory patients that presented themselves at 2 vascular surgery outpatient clinics.

Subjects: A total of 970 patients with new symptoms of PAD or with an exacerbation of existing PAD symptoms that required clinical evaluation and treatment (Rutherford Grade I) were eligible, 884 consented and were included between March 2006 and November 2010. We report on 505 patients in the current study.

Main outcome measures: Prior to patients' initial PAD evaluation, the Short Form 12, Physical Component Scale (PCS) was administered to measure health status. Anatomical lesion location (proximal vs. distal) was derived from duplex ultrasounds. PCS scores, lesion location, and site were evaluated as determinants of receiving invasive (endovascular, surgery) vs. non-invasive treatment ≤1 year following diagnosis in Poisson regression analyses, adjusting for demographics, ankle-brachial index, and risk factors.

Results: Invasive treatment as a first-choice was offered to 167 (33%) patients. While an association between poorer health status and invasive therapy was found in unadjusted analyses (RR=0.98, 95%CI 0.97-1.00, P=.011); proximal lesion location (RR=3.66, 95%CI 2.70-4.96, P<.0001) and site (RR=1.69, 95%CI 1.11-2.58, P=.014) were independent predictors of invasive treatment referral in the final model.

Conclusions: One third of patients were treated invasively following PAD diagnosis. Patients' health status was considered in providers' decision to refer patients for invasive treatment, but having a proximal lesion was the strongest predictor. This study also found some important first indications of site variations in offering invasive treatment among patients with PAD. Future work is needed to further document these variations in care.

INTRODUCTION

Treatment for symptomatic peripheral arterial disease (PAD) in the lower extremities is targeted at symptom relief and cardiovascular risk management.[1] While a myriad of treatments are available for PAD consisting of strategies such as supervised exercise therapy, optimal pharmacological management, and widely adopted invasive options like percutaneous transluminal angioplasty (PTA),[2-4] current treatment guidelines explicitly state to preferentially treat patients with Rutherford Grade I non-invasively, and promote supervised exercise therapy.[5-7]

Current guidelines additionally mention, however, that patients' health status and the anatomic lesion location they present with are important considerations to take into account in the clinical decision-making process to refer patients with PAD for invasive treatment.[5-7] In the field of PAD, however, there are virtually no studies available that examined to what degree these aspects are actually being weighed in the decision to refer patients for invasive treatment in real-world clinical practice and to what degree the threshold for this decision differs across institutions. In addition, it remains unclear whether patients in whom we expect the highest benefit – those with the highest disease burden – are more likely to receive invasive therapy,[4] as compared with those who are experiencing a minimal disease burden.

To address these gaps in knowledge, this study aimed to evaluate whether patients' physical health status, the anatomic lesion location for which they seek treatment, as well as the hospital to which patients present to, are indeed important factors in the referral of patients for invasive treatment for their PAD symptoms. We examined these associations in a cohort of patients with Rutherford Grade I, who were evaluated for newly diagnosed PAD or for an exacerbation of existing symptoms of PAD in a real-world clinical setting. Ideally, we expect that patients who present with favorable risk-benefit lesions (proximal lesions) or patients who have a lower physical health status will be more likely to be referred for invasive treatment as compared with those having more unfavorable risk-benefit lesions (distal lesions) or a better health status.[2, 6, 8, 9]

Addressing these questions seem to be particularly useful in an era where appropriateness criteria for invasive procedures in PAD are still lacking, and the use of costly endovascular procedures continue to rise against a background of tightening budgets for health care.[10, 11]

METHODS

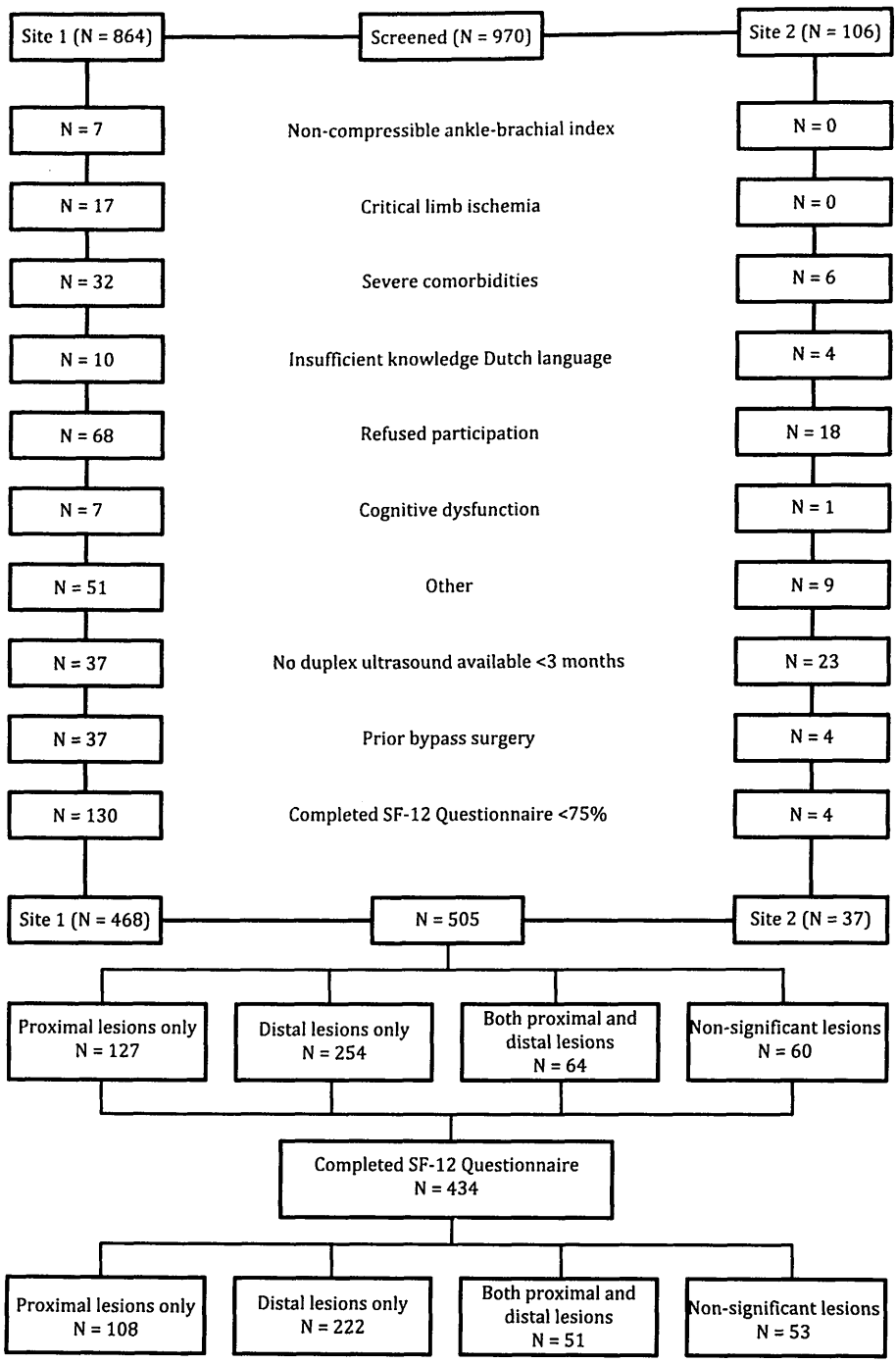
Patients and study design

A total of 1190 patients were screened, 970 were eligible, 884 consented and 505 PAD patients were included (See Figure 1 for overview of exclusion reasons). They were consecutively enrolled within an ongoing prospective observational study for patients that present themselves at 2 vascular surgery outpatient clinics (St. Elisabeth Hospital and TweeSteden Hospital, Tilburg, the Netherlands) with new onset or an exacerbation of PAD symptoms that require clinical evaluation. The cohort under study had 1-year follow-up data available and was enrolled between March 1, 2006 and November 31, 2010. Inclusion criteria were a resting ankle-brachial index (ABI) $\leq$0.90 or a decrease in post-exercise ABI $\geq$15%. Exclusion criteria were a non-compressible ABI ($\geq$1.30), critical limb ischemia, severe cognitive impairment, or severe psychiatric or somatic comorbidities (e.g., psychosis or active oncological treatment), insufficient knowledge of the Dutch language, and other reasons (e.g., treatment for PAD started prior to inclusion in the present study, participation in another study). Because physical health status and anatomical lesion location were variables of interest in this study, participants were additionally excluded if: baseline health status information on the Short Form 12 (SF-12) had >25% missing values, no pre-procedural duplex ultrasound examination was available in patients' medical records within 3 months prior to or after enrollment, or they previously underwent lower-extremity bypass surgery. In the latter case, categorizations of arterial lesions according to pre-defined segments on duplex ultrasound examinations were not feasible.[12]

Vascular laboratory assessments were performed as part of the diagnostic work-up in all participants at baseline and included ABI assessments at rest and after a treadmill walking test in both legs, as well as clinical guided duplex ultrasound examinations. All participants were clinically evaluated by vascular surgeons through a thorough-history taking and physical examination. Patients completed an interview and self-report questionnaires at baseline to document information on demographics, their self-reported physical health status, and psychological factors. Information on risk factors, and medication use was abstracted from patients' medical records upon enrollment.

Likewise, information on 1-year treatment practices was retrieved throughout the year following diagnosis. The study was approved by the local ethics committee of each participating institution. Written informed consent was provided by all participants. Since the study was observational in nature, participation did not impact the type of treatment patients would receive.

Figure 1 - Overview of the study population.



MEASURES

Treatment strategies

Information on treatment strategies offered during the year following enrollment was documented through medical chart abstraction. Both enrolling sites had access to a variety of treatment options including non-invasive options consisting of a formal supervised exercise therapy program; pharmacotherapy (e.g., aspirin, anticoagulants, and statins); and smoking-cessation counseling. Patients were considered to have had non-invasive treatment if no hospital admissions for vascular reasons in the lower-extremities were documented within the year following enrollment. Lower-extremity invasive treatment strategies included lower-extremity PTA (with or without stents), endarterectomy, and bypass surgery. In our analyses, we discriminated between the *first-choice treatment* that patients were referred to directly following diagnosis that may have included invasive vs. non-invasive treatment; and the *final treatment* that patients eventually received during the 1-year following enrollment (to capture information on potential cross-overs from non-invasive to invasive treatment).

Health status

Pre-procedural physical health status was measured by a Dutch language version of the SF-12, a 12-item generic health status instrument that has been widely used in cardiovascular populations.[2, 13] We derived Physical Component Summary (PCS) scores (mean=50, SD=10, range 0-100) that were standardized against the general Dutch population norms.[14] Higher scores indicated better physical functioning.

Duplex ultrasound examination protocol

As part of the diagnostic evaluation, the treating vascular surgeon ordered a clinical-guided duplex ultrasound examination performed by trained vascular technicians using the Toshiba Xario (Xario XG; Toshiba Medical Systems Europe, Zoetermeer, the Netherlands) to derive lesion information (i.e., anatomical lesion location, number of lesions, and peak systolic velocity (PSV [cm/sec]) ratio). A detailed description of the duplex ultrasound protocol has been published elsewhere.[12]

Prior to the analyses, a team of 3 physicians (surgical fellow and 2 vascular surgeons) read the duplex ultrasounds to categorize the anatomical location of the peripheral arterial lesions. Proximal and distal lesions were scored: proximal lesions included significant lesions within the aortoiliac segments.[12] Distal lesions included significant lesions within the femoropopliteal segments and crural segments.[12]

Lesions with a PSV ratio ≥2.5 or occlusions were considered significant.[12] The combined color and pulsed wave Doppler has a 87-88% sensitivity, and 95-99% specificity for detecting significant arterial lesions in patients with lower-extremity PAD as compared with gold standard angiography.[15]

Ankle-brachial index

Vascular technicians measured patients' ABI at rest and following a distance-limited (1000 meters) treadmill test to confirm PAD diagnosis using a handheld Doppler instrument (Imexlab 9000; Imex Medical Systems Inc, Golden Colorado). From this protocol, patients' pain-free walking was also derived. An abnormal ABI was defined as having a resting ABI of ≤0.90 or a post-exercise ABI decrease of ≥15% as compared with the resting ABI.[12]

Cardiovascular history, clinical factors, and medication use

Patients' medical records were abstracted to document a cardiac history (angina, myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, congestive heart failure), cerebrovascular history (stroke, transient ischemic attack), clinical factors (current smoking, diabetes mellitus, dyslipidemia, hypertension, body mass index [BMI, kg/m^2], chronic obstructive pulmonary disease, renal dysfunction, back pain, knee or hip osteoarthritis), and history of lower-extremity procedures (PTA or endarterectomy). Medical records were also abstracted to document patients' medication use following vascular diagnostic work-up. Claudication medications (e.g., Cilostazol) are not approved or distributed in the Netherlands and information on these medications is not included in this study.

Demographic, socioeconomic, and psychological factors

Patients' age and sex was derived from their medical records; sociodemographic information was obtained by self-report questionnaires and included marital status (partner vs. no partner), educational background (greater than high school education vs. less), and working status (active vs. non-active). Additionally, the presence of a distressed (Type D) personality was assessed by the DS14, an instrument that measures the joint tendency socially inhibition and negative affectivity. Scores ≥10 on both subscales denotes a Type D personality.[16] Finally, the presence of clinically relevant anxiety and depression symptoms were verified by the Hospital Anxiety and Depression Scale (HADS), for which a criterion of scores ≥8 was adopted on both subscales.[17]

Statistical analysis

Baseline patient characteristics were described for the total population and compared by first-choice treatment strategy (invasive vs. non-invasive treatment). Potential treatment considerations were described by first-choice and final treatment strategy (invasive vs. non-invasive treatment comparisons for each treatment strategy): (1) patients' physical health status (mean PCS scores for invasive vs. non-invasive treatment); (2) the anatomical lesion location (either proximal, distal lesions or lesions in both locations); and (3) enrollment site (hospital 1 vs. hospital 2). For all descriptive comparisons, Chi-square tests, Student's t-tests and Wilcoxon rank sum tests were used as appropriate.

Missing SF-12 items were assumed to be missing at random and handled by multiple imputation (mean of 5 iterations) if ≥75% of all items were completed by the participants. A sequential, propensity-weighted Poisson regression analysis was constructed to examine the association between treatment considerations (physical health status, anatomic lesion location, and hospital site) and first-choice treatment strategy (invasive vs. non-invasive treatment). A propensity weight was calculated based on all baseline characteristics for the tendency to have missing PCS data (requiring imputation) vs. having complete data for the PCS. The model was sequentially built using the following steps: (1) demographic factors (age, sex), hospital site, and the PCS score; (2) anatomical lesion location (proximal vs. non-proximal); and (3) ABI, prior lower-extremity revascularization (PTA or endarterectomy), pain-free walking distance and cardiovascular risk factors (cardiac history, cerebrovascular history, diabetes mellitus, renal failure, current smoking). The analysis was repeated to determine treatment considerations for the final 1-year treatment strategy (invasive vs. non-invasive treatment). Finally, the area under the receiver operating characteristics curve (AUC) was obtained to derive the c-statistics for both final adjusted models.

Analyses were executed with PASW Statistics 17.0 for Windows (SPSS inc. Chicago, IL) and SAS Software version 9.2 (SAS Institute Inc, Cary, North Carolina). All tests were two-tailed and P-values <.05 were considered statistically significant.

RESULTS

Baseline characteristics

Of the 505 patients included in the study, 167 (33%) received invasive treatment as first-choice treatment strategy whereas 338 (67%) were initially referred to non-invasive treatment.

Table 1 presents the baseline characteristics of the total cohort (n=505), and stratified by first-choice treatment strategy (invasive vs. non-invasive). Patients receiving invasive treatment were more likely to be younger, to have an active working status and a lower BMI as compared with those receiving non-invasive treatment. Additionally, they were less likely to receive aspirin upon PAD diagnosis and their resting ABI was lower. Patients who were initially treated invasively were also more likely to have proximal lesions.

For reasons of completeness, patients' baseline characteristics were also compared by enrollment site (Appendix 1). No major differences were noted (Effect sizes were small: range Cramér's V 0.090-0.113 for prior angina, current smoking, overall anticoagulant use and aspirin use. Cohen's D was 0.21 for pain-free walking distance).

Treatment considerations

Whereas 167 (33%) patients were initially referred for invasive treatment as a first-choice treatment strategy, ultimately, 198 (40%) patients were treated invasively, meaning that an additional 31 patients (6%) received invasive treatment (Table 2).

Patients who were referred for invasive options were more likely to have lower health status scores as compared with patients who did not undergo invasive treatment as their first-choice treatment (mean PCS scores: 37±9 vs. 40±10, P=.008). The same pattern was observed for 1-year final treatment referral (mean PCS scores: 38±10 vs. 40±10, P=.056) (Figure 2a).

A total of 131 (26%) patients presented with proximal lesions, 254 (50%) had distal lesions, and 64 (13%) presented with both proximal and distal lesions upon diagnosis. Patients with proximal lesions were more likely to be referred for invasive treatment as a first-choice treatment as compared with patients without proximal lesions (69% vs. 21%, P<.0001); this remained the same for the final 1-year treatment (76% vs. 26%, P<.0001) (Figure 2b). In contrast, first-choice as well as final invasive treatment referral was less likely in patients with distal lesions as compared with those having no distal lesions (first-choice invasive treatment 16% vs. 51%, P<.0001; 1-year final invasive treatment 22% vs. 57%, P<.0001). Patients with both proximal and distal lesions more often received invasive treatment as a first-choice (58% vs. 30%, P<.0001) and final treatment option (63% vs. 36%, P<.0001) as compared with who were without lesions in both locations.

A total of 468 patients (93%) were enrolled from hospital site 1 and 37 patients (7%) from hospital site 2. First-choice and 1-year final treatment practices stratified by hospital site are presented in Figure 2c and illustrate that invasive treatment referral was less common in hospital 1 as compared with hospital 2 (first-choice invasive treatment 32% vs. 49%, P=.036; 1-year final invasive treatment 38% vs. 56%, P=.055).

Table 1 - Baseline characteristics of the total sample and stratified by first-choice treatment strategy.

	Total sample	First-choice treatment strategy		
	(n=505)	Invasive (n=167)	Non-invasive (n=338)	P-value
Demographics				
Age, mean (SD, range) years	64.7 (9.7, 37-92)	**62.6 (9.8)**	**65.8 (9.5)**	**<.0001**
Male sex, n (%)	324 (64.2)	105 (62.9)	219 (64.8)	.67
Socioeconomic factors				
No partner, n (%)	123 (24.5)	35 (21.2)	88 (26.0)	.24
Less than high school education, n (%)	127 (25.5)	46 (28.0)	81 (24.2)	.35
Working full- or part time, n (%)	135 (27.6)	**54 (33.3)**	**81 (24.8)**	**.046**
Cardiovascular history				
Angina pectoris, n (%)	69 (13.7)	17 (10.2)	52 (15.4)	.11
Myocardial infarction, n (%)	85 (16.8)	23 (13.8)	62 (18.3)	.20
Coronary artery bypass graft surgery, n (%)	60 (11.9)	15 (9.0)	45 (13.3)	.16
Percutaneous coronary intervention, n (%)	45 (8.9)	12 (7.2)	33 (9.8)	.34
Congestive heart failure, n (%)	20 (4.0)	3 (1.8)	17 (5.0)	.08
Stroke, n (%)	38 (7.5)	14 (8.4)	24 (7.1)	.61
Transient ischemic attack, n (%)	43 (8.5)	10 (6.0)	33 (9.8)	.15
Clinical factors				
Smoking, n (%)	250 (49.5)	93 (55.7)	157 (46.4)	.051
Diabetes mellitus, n (%)	121 (24.0)	38 (22.8)	83 (24.6)	.66

	Total sample (n=505)	First-choice treatment strategy		
		Invasive (n=167)	Non-invasive (n=338)	P-value
Table 1 (Continued)				
Hypercholesterolemia, n (%)	342 (67.7)	111 (66.5)	231 (68.3)	.67
Hypertension, n (%)	308 (61.0)	95 (56.9)	213 (63.0)	.18
Body mass index, mean (SD)	26.7 (4.6)	**25.9 (3.6)**	**27.1 (5.0)**	**.001**
Chronic obstructive pulmonary disease, n (%)	79 (15.6)	23 (13.8)	56 (16.6)	.42
Renal dysfunction, n (%)	38 (7.5)	10 (6.0)	28 (8.3)	.36
Back pain, n (%)	75 (14.9)	31 (18.6)	44 (13.0)	.10
Hip or knee pain, n (%)	105 (20.8)	39 (23.4)	66 (19.5)	.32
Medication use				
Overall anticoagulants, n (%)	447 (88.5)	**138 (82.6)**	**309 (91.4)**	**.004**
Aspirin, n (%)	406 (80.4)	**124 (74.3)**	**282 (83.4)**	**.014**
Anticoagulants, n (%)	82 (16.2)	28 (16.8)	54 (16.0)	.82
Statins, n (%)	416 (82.4)	130 (77.8)	286 (84.6)	.06
Beta blocker, n (%)	210 (41.6)	60 (35.9)	150 (44.4)	.07
Diuretics, n (%)	116 (23.0)	32 (19.2)	84 (24.9)	.15
ACE inhibitor, n (%)	159 (31.5)	54 (32.3)	105 (31.1)	.77
Calcium antagonist, n (%)	106 (21.0)	29 (17.4)	77 (22.8)	.16
Nitroglycerin, n (%)	44 (8.7)	9 (5.4)	35 (10.4)	.06
Digoxin, n (%)	9 (1.8)	2 (1.2)	7 (2.1)	.49

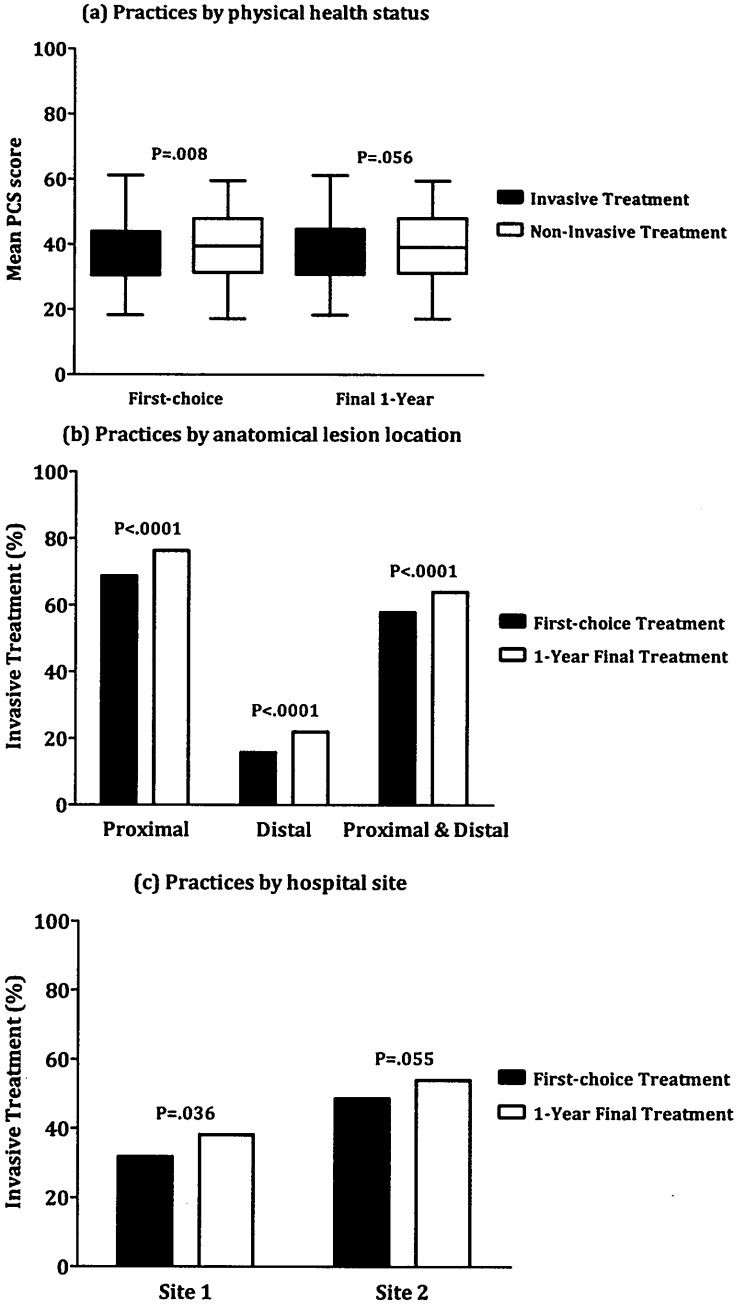
	Total sample (n=505)	First-choice treatment strategy		
		Invasive (n=167)	Non-invasive (n=338)	P-value
Table 1 (Continued)				
Antiarrhythmics, n (%)	15 (3.0)	5 (3.0)	10 (3.0)	.98
Antidepressives, n (%)	29 (5.7)	13 (7.8)	16 (4.7)	.17
Anxiolytics, n (%)	20 (4.0)	3 (1.8)	17 (5.0)	.08
Hypnotics, n (%)	27 (5.3)	10 (6.0)	17 (5.0)	.65
Vascular laboratory assessment				
Pain-free walking distance, median (SD), m	80.0 (128.9)	70.0 (131.3)	80.0 (127.6)	.14
Resting ABI, mean (SD)*	0.66 (0.17)	**0.63 (0.17)**	**0.67 (0.16)**	**.011**
Prior lower-extremity revascularization				
Endovascular	54 (10.7)	24 (14.4)	30 (8.9)	.06
Endarterectomy	9 (1.8)	1 (0.6)	8 (2.4)	.16
Psychological factors				
Depression, n (%)	143 (28.5)	47 (28.3)	96 (28.7)	.94
Anxiety, n (%)	126 (25.1)	45 (27.1)	81 (24.2)	.48
Type D personality, n (%)	111 (22.1)	42 (25.1)	69 (20.5)	.24

Abbreviations: SD = standard deviation; ACE inhibitor = angiotensin-converting-enzyme inhibitor; ABI = ankle-brachial index; *lowest ABI measured, †not significant.

Table 2 - Treatment practices of the total sample and stratified by 1-year treatment strategy.

	Total sample (n=505)	1-year treatment strategy		
		Invasive (n=198)	Non-invasive (n=307)	P-value
Lower-extremity revascularization				
Endovascular, n (%)	158 (31.3)	**158 (79.8)**	**0 (0.0)**	**<.0001**
Surgery, n (%)	55 (10.9)	**55 (27.8)**	**0 (0.0)**	**<.0001**

Figure 2 - Treatment considerations for first-choice and final treatment strategies. (a) Mean PCS scores are presented by first choice and 1-year invasive treatment rates; and first choice and 1-year invasive treatment rates are presented by (b) anatomical lesion location, and (c) hospital site.



Determinants of invasive treatment: Multivariable results

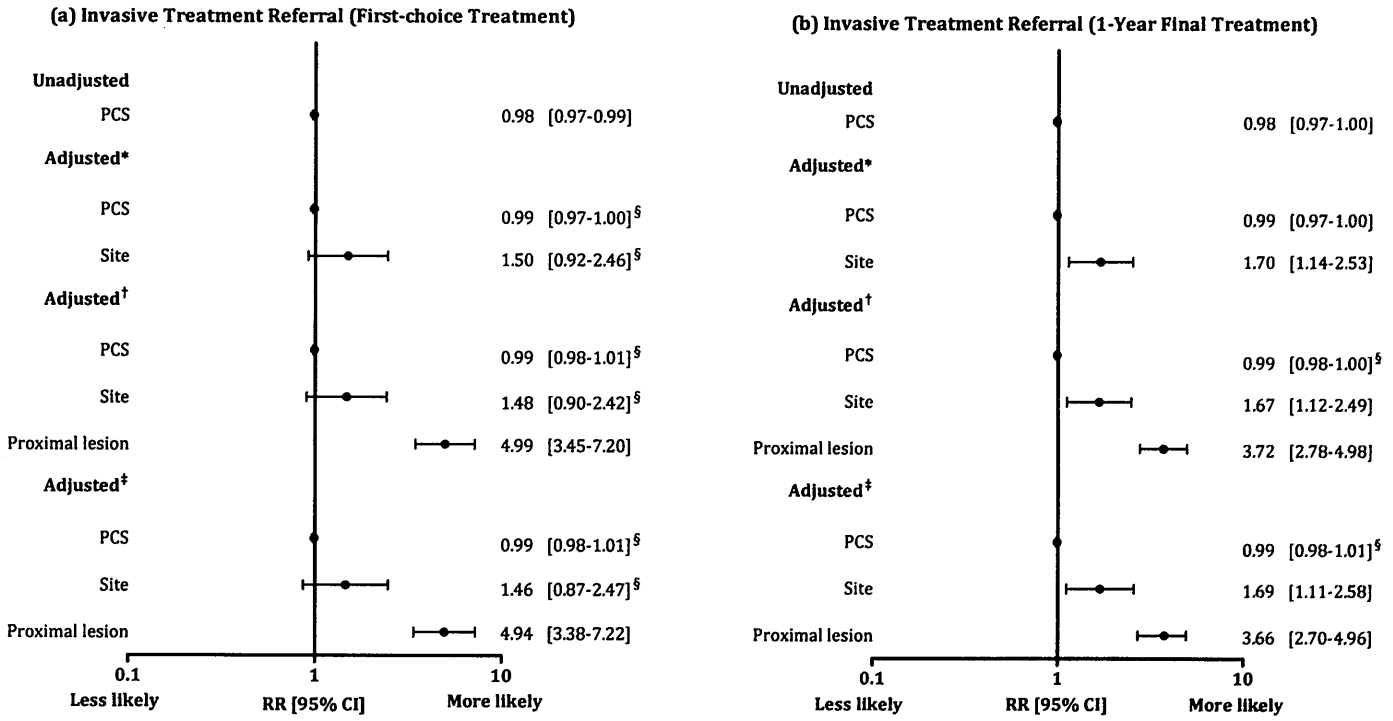
Multiple imputation was applied in 71 cases to calculate PCS scores. Patients' pain-free walking distance was missing in 6 cases. There was no other missing covariate data.

Patients with a better health status were less likely to be referred for invasive options as first-choice treatment as compared with those having a poorer health status in the unadjusted model (unadjusted RR=0.98, 95%CI 0.97-0.99, P=.033), but was later explained by the presence of proximal lesions (P<.0001) (Figure 3a). Having a proximal lesion (RR=4.94, 95%CI 3.38-7.22, P<.0001) was independently associated with a higher chance of being referred for first-choice invasive treatment in the final adjusted model (Figure 3a).

Figure 3b replicates the results for the 1-year final treatment referral including 493 patients who were alive at 1-year follow-up. Similarly, patients with a better health status were less likely to be referred for invasive options in the unadjusted model (RR=0.98, 95%CI 0.97-1.00, P=.011), as compared with patients who had poorer health status. Proximal lesion location (RR=3.66, 95%CI 2.70-4.96, P<.0001) and hospital site (RR=1.69, 95%CI 1.11-2.58, P=.014) were independently associated with 1-year invasive treatment referral in the final adjusted model (Figure 3b). Full model results are presented in Appendix 2.

The c-statistic was 0.82 (95%CI 0.79-0.86, P<.0001) for the final model predicting first-choice treatment and 0.82 (95%CI 0.78-0.86, P<.0001) for the 1-year model.

Figure 3 – Determinants of (a) first-choice and (b) final treatment strategies (invasive treatment vs. non-invasive treatment options [reference]).



The (un)adjusted Relative Risks (RR) and 95% Confidence Intervals (CI) are presented. Abbreviations: PCS = physical component scale. The model was sequentially adjusted for: *PCS, predicted probability, hospital (site), demographics (age, sex); †anatomical lesion location (proximal vs. non-proximal); ‡ankle-brachial index, prior lower-extremity revascularization, pain-free walking distance and cardiovascular risk factors (cardiac history, cerebrovascular history, diabetes mellitus, renal failure, smoking). §Not significant.

DISCUSSION

Despite the lack of appropriateness criteria in PAD management, there seems to be a consensus to preferentially maximizing non-invasive treatment strategies first before offering invasive options for patients with symptomatic PAD.[5-7] While factors such as response to non-invasive treatment, anatomical lesion location, quality of life and patient preferences may seem to be relevant factors to take into account when making a decision to refer patients for invasive treatment,[5-7] it is unclear how these factors are actually being valued in the real-world clinical-decision making process and whether rates differ with regards to invasive treatment referrals across hospital sites for patients with a comparable clinical and symptom profile. The present study evaluated the association between patients' physical health status, anatomical lesion location, and hospital site and invasive treatment referral in patients with new onset or an exacerbation of pre-existing PAD symptoms (Rutherford Grade I) at 2 vascular surgery offices. Our results demonstrate that – within the year following their initial PAD evaluation – more than one third of the total population was referred for invasive options as a first-choice treatment strategy. Invasive treatment was more offered to those with a poorer physical health status. Invasive treatment was about 4 times more applied in patients having proximal lesions vs. distal lesions and nearly twice as often in one hospital site vs. the other. Furthermore, both final models reached good discriminative accuracy for the prediction of invasive treatment referral.

While prior registries demonstrate that peripheral revascularizations are major contributors to high hospitalization rates and raising cumulative health care costs,[10] there are no studies that systematically evaluate what factors are weighed in the health care providers' decision before referring patients to such costly invasive options. Likewise, it is unknown whether such decisions and associated invasive treatment rates vary across institutions. Recently, such site variations in the intensity of care have been observed in patients with more advanced stages of PAD and other vascular conditions, suggesting that it is worthwhile and much needed to also evaluate treatment variations in earlier stages of the disease as well.[18, 19]

While preliminary findings suggest that patients' self-reported physical health status matters when choosing an invasive treatment modality in PAD,[9] it is currently unknown whether favorable risk-benefit lesions (proximal lesions)[5-7] and site variations are other important factors that help clinicians decide to refer patients for invasive options. Our study is unique because it used real-world clinical data from 2 vascular surgery offices to examine these questions in a homogenous cohort of ambulatory PAD patients.

According to practice guidelines, invasive treatment as a first-choice option in patients with symptomatic PAD may be considered in patients presenting with favorable risk-benefit lesions (proximal disease).[5-7] In addition, quality of life considerations are another factor that needs to be considered. Claudication symptoms that are impairing patients' daily functioning are important reasons[4] to offer an invasive treatment, as higher benefits are expected in those patients. While we saw a strong association between lesion location and receipt of invasive treatment, the observed (un)adjusted associations for health status and invasive treatment referral were very weak, suggesting that invasive treatment is not consistently offered in patients who might need it the most.

In support of this latter hypothesis, we provided – as one of the first in its kind in patients with symptomatic PAD – preliminary evidence to suggest that variations in care not only exist based on patient characteristics but are also explained by practice variations across institutions. Patients with similar symptoms and clinical profiles (Appendix 1) going to one hospital were almost twice as often invasively treated, as compared with the other hospital. A long-standing tradition of documenting site variations in care and developing appropriateness criteria for procedures[20] has been established in most cardiac conditions,[20-22] but this effort is still in its infancy for PAD. With the hopes that our study may contribute to the field of quality of care research in PAD, along with efforts from newer procedural registries (i.e., BMC2 PVI registry[23] or the Society for Vascular Surgery (SVS) Vascular Registry®[24]) documenting the quality of care, future studies need to document procedural variability's and treatment indications.

Finally, the elements studied in this manuscript should not be the only thriving factors in the decision-making process, but patient preferences and a discussion about which outcomes are most valued and risks that patients are willing to take, should also be part of the discussion.

Other contextual factors that were not explicitly studied in this work, but are nevertheless important in optimizing the decision-making process include access to a variety of treatment options that are promoted in PAD guidelines and performance measures.[5, 7, 25] For instance, access to and insurance coverage for supervised exercise training programs was available to clinicians and patients at the time of conducting this study in the Netherlands, but may not be readily available in other countries. Second, knowledge on what health status outcomes patients can expect from different treatment modalities given their personal clinical profile is missing and future comparative effectiveness research with a focus on health status is warranted in order to provide health care providers and their patients with sufficient information on treatment risks and benefits for each alternative treatment option for lower-extremity PAD.

Some study limitations should be addressed before interpreting our results. Despite observing site variations, it should be noted that only 2 institutions were included with a difference in sample size. The 2 study populations, however, were comparable for baseline characteristics. Furthermore, we were unable to evaluate provider variability due to the fact that patients may have been seen by different vascular surgeons and that the enrolling vascular surgeon was not necessarily the one that referred patients for their treatment. In addition, patient preferences regarding the decision to undergo invasive treatment were not directly measured and it is unknown how these may have impacted the decision-making process. Finally, our results may only be generalizable to the Dutch PAD population due to differences in reimbursement rates, access to universal health care and formal for supervised exercise training facilities.

In conclusion, this study demonstrates that having proximal lesions is being considered when referring patients for invasive treatment in lower-extremity PAD, whereas poorer health status only marginally explained why clinicians refer patients for invasive treatment. In contrast, site variability was another factor that explains variations in referral rates. Against a background of tightening health care budgets and a disproportionate high morbidity and economic burden in patients with PAD,[10, 26] it is important to continue to focus on quality of care considerations and developing shared-decision making models to prioritize care to those patients that need it the most.

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APPENDIX 1 - Baseline characteristics stratified by hospital site.

	Site 1 (n = 468)	Site 2 (n = 37)	P-value
Demographics			
Age, mean (SD, range) years	64.7 (9.8)	65.3 (8.5)	.68
Male sex, n (%)	298 (63.7)	26 (70.3)	.42
Socioeconomic factors			
No partner, n (%)	352 (75.5)	28 (75.7)	.99
Less than high school education, n (%)	117 (25.3)	10 (27.8)	.74
Working full- or part time, n (%)	127(28.0)	8 (22.9)	.51
Cardiovascular history			
Angina pectoris, n (%)	**68 (14.5)**	**1 (2.7)**	**.044**
Myocardial infarction, n (%)	82 (17.5)	3 (8.1)	.14
Coronary artery bypass surgery, n (%)	55 (11.8)	5 (13.5)	.79
Percutaneous coronary intervention, n (%)	43 (9.2)	2 (5.4)	.76
Congestive heart failure, n (%)	18 (3.8)	2 (5.4)	.65
Stroke, n (%)	33 (7.1)	5 (13.5)	.18
Transient ischemic attack, n (%)	40 (8.5)	3 (8.1)	1.00
Clinical factors			
Smoking, n (%)	**239 (51.1)**	**11 (29.7)**	**.012**
Diabetes mellitus, n (%)	111 (23.7)	10 (27.0)	.65
Hypercholesterolemia, n (%)	317 (67.7)	25 (67.6)	.98
Hypertension, n (%)	289 (61.8)	19 (51.4)	.21
Body mass index (BMI), mean (SD)	26.8 (4.7)	26.3 (3.7)	.46
COPD, n (%)	73 (15.6)	6 (16.2)	.92
Renal dysfunction, n (%)	34 (7.3)	4 (10.8)	.51
Back pain, n (%)	66 (14.1)	9 (24.3)	.09
Hip or knee pain, n (%)	99 (21.2)	6 (16.2)	.48
Medication use			
Overall anticoagulants, n (%)	**419 (89.5)**	**28 (75.7)**	**.011**
Aspirin, n (%)	**382 (81.6)**	**24 (64.9)**	**.013**
Anticoagulants, n (%)	78 (16.7)	4 (10.8)	.35
Statins, n (%)	384 (82.1)	32 (86.5)	.50

	Site 1 (n = 468)	Site 2 (n = 37)	P-value
Appendix 2 (Continued)			
Beta blocker, n (%)	196 (41.9)	14 (37.8)	.63
Diuretics, n (%)	107 (22.9)	9 (24.3)	.84
ACE inhibitor, n (%)	147 (31.4)	12 (32.4)	.90
Calcium antagonist, n (%)	99 (21.2)	7 (7.3)	.75
Nitroglycerin, n (%)	42 (9.0)	2 (5.4)	.76
Digoxin, n (%)	9 (1.9)	0 (0.0)	1.00
Antiarrhythmics, n (%)	12 (2.6)	3 (8.1)	.09
Antidepressives, n (%)	29 (6.2)	0 (0.0)	.26
Anxiolytics, n (%)	19 (4.1)	1 (2.7)	1.00
Hypnotics, n (%)	27 (5.8)	0 (0.0)	.25
Vascular laboratory assessment			
Pain-free walking distance, median (SD), m	**70.0 (132.0)**	**100.0 (74.3)**	**.002**
Resting ABI, mean (SD)*	0.66 (0.16)	0.69 (0.21)	.40
Prior lower-extremity revascularization			
Endovascular, n (%)	51 (10.9)	3 (8.1)	.60
Endarterectomy, n (%)	8 (1.7)	1 (2.7)	.66
Psychological factors			
Depression, n (%)	130 (28.0)	13 (35.1)	.36
Anxiety, n (%)	115 (24.8)	11 (29.7)	.51
Type D personality, n (%)	103 (22.1)	8 (22.2)	.98

Abbreviations: SD = standard deviation, COPD = chronic obstructive pulmonary disease, ACE inhibitor = angiotensin-converting-enzyme inhibitor, ABI = ankle-brachial index, *lowest ABI measured.

APPENDIX 2 – Full model results for determinants of treatment strategies (invasive treatment vs. non-invasive treatment options [reference]).

	First-choice treatment			1-year final treatment		
	RR	**95% CI**	**P-value**	**RR**	**95% CI**	**P-value**
PCS	0.99	0.98-1.01	.37	0.99	0.98-1.01	.23
Predicted probability	0.82	0.16-4.30	.81	0.86	0.22-3.40	.83
Site	1.46	0.87-2.47	.16	**1.69**	**1.11-2.58**	**.014**
Age	1.00	0.98-1.02	.76	1.00	0.98-1.01	.71
Male sex	1.16	0.83-1.64	.39	1.06	0.79-1.41	.71
Proximal lesion	**4.94**	**3.38-7.22**	**<.0001**	**3.66**	**2.70-4.96**	**<.0001**
Ankle-brachial index	1.00	0.99-1.01	.48	1.00	0.99-1.01	.39
Prior revascularization*	1.17	0.75-1.82	.49	1.16	0.80-1.68	.45
PFWD	0.99	0.83-1.18	.89	0.95	0.81-1.12	.55
Cardiac history†	0.96	0.66-1.41	.85	1.03	0.75-1.41	.88
Cerebrovascular history‡	0.95	0.58-1.55	.84	0.86	0.56-1.31	.47
COPD	0.96	0.60-1.53	.86	0.92	0.61-1.37	.66
Diabetes mellitus	1.19	0.82-1.74	.37	1.08	0.78-1.49	.66
Renal failure	0.92	0.47-1.79	.81	1.14	0.68-1.91	.61
Smoking	1.02	0.72-1.43	.93	0.94	0.71-1.26	.68

Abbreviation: PCS = physical component score, PFWD=pain-free walking distance, COPD=chronic obstructive pulmonary disease *Prior revascularization includes lower-extremity percutaneous transluminal angioplasty and endarterectomy. †Cardiac history includes: prior angina, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, and heart failure. ‡Cerebrovascular history includes: prior stroke and transient ischemic attack.

Chapter 4

Extensiveness of lesions

in lower-extremity peripheral arterial disease

3.2-year risk of multiple cardiovascular events

4

M. van Zitteren, J. Denollet, P.G. Jones, J.A. Spertus, J.M. Heyligers, M.J. Nooren, P.W. Vriens, K.G. Smolderen. Extensiveness of lesions in lower-extremity peripheral arterial disease: 3.2-year risk of multiple adverse events. *Submitted.*

ABSTRACT

Objectives: To examine whether having multiple versus isolated lower-extremity peripheral arterial disease (PAD) lesions is associated with increased risks of an adverse prognosis.

Background: While PAD patients are known to be at increased risk of an adverse prognosis, simple techniques to further risk stratify PAD patients would be clinically useful. A plausible, but unexplored, factor to predict such risk would be a greater disease burden, manifested by having multiple lower-extremity lesions.

Methods: A prospective cohort of 756 patients with newly diagnosed PAD underwent duplex ultrasound testing to determine the number of lower-extremity lesions. Cox regression models examined the independent association of lesion number (≥3 and 2 vs. 1) and adverse prognosis (lower-extremity amputation; congestive heart failure; non-fatal stroke or myocardial infarction; transient ischemic attack; unstable angina; and mortality), after adjusting for demographic and clinical risk factors. These analyses were replicated using an advanced Cox-based model for multiple events.

Results: A total of 173 (23%) patients had ≥3 lesions, 197 (26%) had 2 lesions, and 386 (51%) had 1 lesion. After a median of 3.2 years of follow-up, patients with ≥3 lesions had an increased risk of experiencing a first adverse event (adjusted HR=1.56, 95%CI 1.09-2.25, P=.016), and an increased risk of having multiple events (adjusted HR=1.66, 95%CI 1.21-2.28, P=.001). Patients with 2 lesions had a similar prognosis to those with only one.

Conclusions: Among patients with PAD, a greater number of lesions is associated with an increased risk of an adverse prognosis over 3 years of follow-up. Assessing the extensiveness of lower-extremity lesions might serve as a simple risk stratification tool at initial PAD diagnosis.

INTRODUCTION

Patients with peripheral arterial disease (PAD) are a vulnerable population because they not only experience functional impairment,[1, 2] but also face an excess risk of an adverse prognosis (e.g., myocardial infarction [MI], unstable angina, stroke, heart failure, lower-extremity amputation and death) due to concomitant coronary and cerebrovascular disease.[3-6]

This risk of experiencing an adverse prognosis is applicable to the whole spectrum of PAD patients, and therefore mandates aggressive cardiovascular risk factor control through the prescription of statins, antiplatelet therapy, and smoking cessation therapy.[7-9] Among patients with PAD, however, there have been few efforts to further risk stratify patients at the time of their initial presentation. A simple marker of a worse prognosis could be the extent of their disease, as suggested by the number of obstructive lesions identified at presentation. The clinical logic is that a greater number of lesions may reflect a more aggressive disease process, not only in the peripheral arteries, but also in the coronary and cerebral vasculature as well. Risk stratifying PAD patients may be clinically useful so that more intensive follow-up and more aggressive treatment might be considered, including a more thorough work-up and screening for occult coronary or cerebrovascular disease.

Although it is expected that patients presenting with multiple lower-extremity arterial lesions are more likely to be at increased risk for having any, or multiple, adverse events than those having a single lesion, this assumption has – surprisingly – never been empirically quantified in patients with PAD.[10] To address this gap in knowledge, our objectives were to document patients' risk of experiencing a *first,* as well as *multiple,* adverse events after an initial PAD diagnosis (Rutherford Grade I) as a function of the number of lower-extremity arterial lesions identified. We additionally explored which type of adverse event (lower-extremity amputation, unstable angina, MI, heart failure, stroke/transient ischemic attack [TIA] or death) would mostly explain patients' adverse risk.

This information could support better quantification of PAD patients' risk for subsequent events, and may provide clinicians with an easy way to risk stratify patients with new onset or worsening symptoms of PAD.

METHODS

Patients and study design

A total of 756 patients with PAD were systematically followed for a median of 3.2 years (±1.6 years; interquartile range [IQR] 1.7-4.5 years). Patients were consecutively enrolled from 2 vascular surgery outpatient clinics (St. Elisabeth Hospital and TweeSteden Hospital, Tilburg, the Netherlands) between March 1, 2006 and October 31, 2011 based on their presentation with new onset symptoms of PAD, or an exacerbation of existing PAD symptoms requiring clinical re-evaluation and treatment. Inclusion criteria for this observational study were an abnormal ankle-brachial index (ABI) at rest (≤0.90) or a decrease in patients' post-exercise ABI ≥15% following a distance-limited treadmill walking test (1000 meters). Patients were excluded from the study if they had a non-compressible ABI (≥1.30), presented with critical limb ischemia, severe cognitive impairment, or severe psychiatric or somatic comorbidities (e.g., psychosis or active cancer treatment), or if they were lacking sufficient knowledge of the Dutch language. Since the focus of this particular study was on the extensiveness of lower-extremity lesions, patients were additionally excluded if no pre-procedural duplex ultrasound examination was available from their medical records within 3 months of their enrollment. An overview of the reasons for exclusions is provided in Appendix 1.

All patients underwent non-invasive vascular laboratory testing as part of their clinical evaluation for PAD including resting and post-exercise ABI measurements, as well as a duplex ultrasound examination. Information on demographic and socioeconomic factors was obtained from patients at baseline through purpose-designed questionnaires and information on clinical factors was collected through medical chart abstraction. Finally, up-to-date vital status information was also retrieved from patients' electronic medical records until January 1, 2012, which contained information on in-hospital deaths and deaths that occurred outside the hospital as records are linked to the regional social security death index of the Tilburg community. Information on deaths occurring outside the Tilburg community was provided by patients' general practitioners. The study was designed in line with the Helsinki Declaration and approved by the local institutional review board of each participating site and all participants provided written informed consent.

MEASURES

Adverse prognosis

The primary outcome of this study was documentation, by hospital or death records, of any of the following major adverse events: (1) PAD-related lower-extremity amputation at any level (i.e., not including traumatic amputations); (2) congestive heart failure; (3) non-fatal stroke or TIA; (4) non-fatal MI or unstable angina; (5) fatal MI or stroke, and (6) other (cardiovascular) causes of death (e.g., cardiac arrest, heart failure, sepsis, exacerbation of chronic obstructive pulmonary disease [COPD], cancer). Data on adverse events were abstracted from patients' medical records and adjudicated by a team of 3 physicians (surgical fellow and 2 vascular surgeons).

Vascular laboratory assessments

Patients' ABI was read from a handheld Doppler instrument (Imexlab 9000; Imex Medical Systems Inc, Golden Colorado) used by trained vascular technicians. Both the ABI at rest and post-exercise were obtained. The exercise protocol included a distance-limited treadmill test (1000 meters) from which the pain-free walking and maximum walking distance were also derived. The ABI was calculated by dividing the highest ankle pressure (posterior tibial artery or dorsalis pedis artery) in each leg by the highest brachial pressure. A resting ABI $\leq$0.90 or decrease in post-exercise ABI $\geq$15% was considered abnormal.

Duplex ultrasound examination protocol

Information on the number of lesions, the anatomical lesion location, and lesion severity, as indicated by the peak systolic velocity ratio (PSV [cm/sec]), was derived from duplex ultrasound examinations prior to the initiation of any treatment. A detailed description of the duplex ultrasound examination protocol has been published previously.[11]

A team of 3 physicians (surgical fellow and 2 vascular surgeons) adjudicated the duplex information to quantify and classify patients by the number of their peripheral arterial lesions. Lesions with a PSV ratio ≥2.5 or total occlusions (no flow, and no PSV ratio could be measured) were considered significant and lesions with a PSV ratio >0-<2.5 were considered non-significant.[11] The number of significant and non-significant lesions was documented from duplex ultrasound readings (i.e., every lesion will be counted as 1 lesion). Lesions were also categorized by their anatomical location including: (1) proximal (aortoiliac segments), (2) distal (femoropopliteal and crural segments), and (3) both proximal and distal lesions. As compared with gold standard angiography, the combined color and pulsed wave Doppler has a sensitivity of 87-88% and specificity of 95-99% for detecting significant arterial lesions in patients with lower-extremity PAD.[12]

Patient characteristics

Information on clinical factors was abstracted from patients' electronic medical records and included cardiovascular history (prior angina, MI, coronary artery bypass graft [CABG], percutaneous coronary intervention [PCI], heart failure stroke, and TIA). Information on other clinical risk factors (current smoking status, diabetes mellitus, hypertension, dyslipidemia, COPD, body mass index [BMI; kg/m^2], renal dysfunction, back pain, and hip or knee osteoarthritis) was also collected and medications that patients were on following their vascular diagnostic work-up. Demographic factors were obtained from patients' medical records and included age and sex. Socioeconomic factors were derived from purpose-designed questions and referred to patients' marital status (no partner vs. partner), education (< high school vs. ≥ high school degree), and work status (active vs. non-active work status).

Statistical analysis

Patients were categorized by the number of significant lower-extremity lesions they presented with derived from the duplex ultrasound readings using the following groups: (a) ≥3 lesions (≥3 lesions with a PSV ratio ≥2.5 and/or total occlusions), (b) 2 lesions (2 lesions with a PSV ratio ≥2.5 and/or total occlusions) and (c) 1 lesion (1 lesion with a PSV ratio ≥2.5, or 1 occlusion, or non-significant lesions with a PSV ratio >0-<2.5). Likewise, these 3 groups were used for the main analyses. Baseline patient characteristics were described for the total population and compared by the 3 groups. Categorical variables were analyzed by the Chi-square test, whereas One-way analysis of variance (ANOVA) was used to analyze continuous variables. Due to power considerations, the association between the number of lesions (≥3 or 2 vs. 1 lower-extremity lesions) and adverse events was analyzed using a composite endpoint (i.e., amputation, unstable angina, MI, heart failure, stroke, TIA, and death). Additionally, stratified analyses examined the association between the number of lesions and adverse event type.

Time-to-first event analysis

Patients were followed for a mean of 3.2 years (±1.6 years; IQR 1.7-4.5 years). and the incidence of adverse events by ≥3, 2 vs. 1 lesions (reference) were plotted by Kaplan-Meier curves and compared with the log-rank test. Risk estimates (hazard ratios [HR] and their 95% confidence intervals [CI]) for the association between having ≥3 or 2 vs. 1 (reference) lower-extremity lesions and experiencing a first major adverse event at 3.2-year follow-up were calculated using a traditional time-to-first event Cox regression model. Multivariable analyses were adjusted for the following *a priori* selected covariates, including: demographics (age, sex), cardiovascular history (angina, MI, PCI, CABG, heart failure, stroke, TIA), other clinical risk factors (BMI, COPD, hypertension, hyperlipidemia, diabetes, renal dysfunction, smoking status), and the presence of proximal lesions vs. non-proximal lesions (reference). Baseline hazards were also stratified by hospital. Effects of continuous variables (age, BMI) were tested for linearity using restricted cubic splines. Proportional hazards assumptions were evaluated using Schoenfeld residuals.

Sensitivity analysis

Similarly, a sensitivity analysis was performed to evaluate the association between having ≥3, 2 vs. 1 lesions (reference) and 3.2-year risk of multiple adverse events - as opposed to the main time-to-first event analysis - using an unadjusted and adjusted Cox-based intensity-elapsed time model including the same covariates as used in the time-to-first event analysis.[13] This model assumes that all events are equally likely to occur, independent from prior events, with the risk for each event starting from 'time zero', the time of initial enrollment.[13] The within-patient correlation was modeled by a frailty term (i.e., a random component to account for within-patient correlation). The mean cumulative incidence of events was also calculated, stratified by the extensiveness of disease (≥3, 2 vs. 1 lesions [reference]).

Event-specific analyses

Given the composite nature of the outcome, a multivariate Cox regression analysis was constructed to evaluate whether the risk associated with lesion extensiveness varied by event type. The model included baseline hazards stratified by event type, an interaction between number of lesions and event type, adjustment for other covariates as described above, and a frailty term to model within-patient correlation.

The follow-up data for adverse events was complete. Covariate data were complete except for BMI, which was missing on 16% of patients. For modeling purposes, missing values of BMI were imputed using single regression imputation on all other available covariates and outcomes. All statistical analyses were performed with SAS Software version 9.3 (SAS Institute Inc, Cary, North Carolina) and R Software version 2.14.1. All tests were two-tailed and statistical significance was considered if P-values were <.05.

RESULTS

Baseline characteristics by number of lesions

Of the 756 included patients, 173 (23%) presented with ≥3 lesions at the initial diagnostic evaluation, 197 (26%) had 2 significant lesions, and 386 (51%) had a non-significant lesion (n=77) or 1 significant lesion (n=309).

Table 1 summarizes patient characteristics for the total study population, and stratified by the number of lower-extremity arterial lesions (≥3, 2, 1 lesions). The mean age of the population was 65 years (±10 years, range 37-92) and 65% were male. Patients with ≥3 lesions were older and more likely to be without a partner, to present with a prior cardiovascular history (angina, MI or TIA) and were more often taking cardiovascular medications (diuretics, ACE inhibitors, nitroglycerin, anticoagulants, digoxin), anti-depressives and hypnotics. Patients having ≥3 lesions more often presented with distal lesions and more often had lesions in both proximal and distal segments. Finally, patients' maximum walking distance, resting ABI, and post-exercise ABI decreased along with the number of lesions detected at presentation.

Adverse events

A total of 245 adverse events occurred among 172 (23%) patients who experienced at least 1 event and among 45 (6%) patients who had at least 2 events during follow-up. Table 2 summarizes the crude cumulative incidence rates stratified by event type; death (n=87) was the most commonly documented event, followed by CVA/TIA (47 events), and MI (37 events).

Table 1 – Baseline characteristics for the total sample, and stratified by extensiveness of lower-extremity peripheral arterial lesions (≥3 vs. 2 vs. 1 lesions).

	Total sample (n=756)	≥3 lesions (n=173)	2 lesions (n=197)	1 lesion (n=386)	P-value
Demographics					
Age (mean ± SD), years	65.0 ± 9.8	**68.0 ± 10.2**	**64.9 ± 9.6**	**63.8 ± 9.5**	**<.001**
Age < 50 years, n (%)	50 (6.6)	**6 (3.5)**	**14 (7.1)**	**30 (7.8)**	**.002**
Age 50 – 69 years, n (%)	430 (56.9)	**82 (47.4)**	**114 (57.9)**	**234 (60.6)**	
Age ≥ 70 years, n (%)	276 (36.5)	**85 (49.1)**	**69 (35.0)**	**122 (31.6)**	
Male sex, n (%)	489 (64.7)	117 (67.6)	136 (69.0)	236 (61.1)	.11
Socioeconomic factors					
No partner, n (%)	162 (21.4)	**51 (34.9)**	**40 (23.7)**	**71 (21.5)**	**.007**
< High school education, n (%)	165 (21.8)	42 (29.2)	45 (26.6)	78 (23.8)	.45
Active working status, n (%)	163 (21.6)	25 (18.2)	48 (28.7)	90 (28.1)	.06
Cardiovascular risk factors					
Prior angina, n (%)	112 (14.8)	**39 (22.5)**	**19 (9.6)**	**54 (14.0)**	**.002**
Prior myocardial infarction, n (%)	140 (18.5)	**48 (27.7)**	**35 (17.8)**	**57 (14.8)**	**.001**
Prior CABG, n (%)	82 (10.8)	26 (15.0)	17 (8.6)	39 (10.1)	.11
Prior PCI, n (%)	70 (9.3)	15 (8.7)	21 (10.7)	34 (8.8)	.73
Heart failure, n (%)	36 (4.8)	9 (5.2)	8 (4.1)	19 (4.9)	.86
Prior TIA, n (%)	66 (8.7)	**24 (13.9)**	**13 (6.6)**	**29 (7.5)**	**.023**

	Total sample (n=756)	≥3 lesions (n=173)	2 lesions (n=197)	1 lesion (n=386)	P-value
Table 1 (Continued)					
Prior stroke, n (%)	59 (7.8)	16 (9.2)	16 (8.1)	27 (7.0)	.64
Clinical factors					
Body mass index (mean ± SD)	26.8 ± 4.9	26.4 ± 4.6	26.5 ± 3.9	27.1 ± 5.5	.25
Smoking, n (%)	375 (49.6)	75 (43.4)	99 (50.3)	201 (52.1)	.16
Diabetes mellitus, n (%)	183 (24.2)	43 (24.9)	47 (23.9)	93 (24.1)	.97
Hyperlipidemia, n (%)	512 (67.7)	126 (72.8)	127 (64.5)	259 (67.1)	.21
Hypertension, n (%)	452 (59.8)	113 (65.3)	115 (58.4)	224 (58.0)	.24
COPD, n (%)	136 (18.0)	29 (16.8)	36 (18.3)	71 (18.4)	.89
Renal dysfunction, n (%)	69 (9.1)	22 (12.7)	18 (9.1)	29 (7.5)	.14
Back pain, n (%)	113 (14.9)	19 (11.0)	34 (17.3)	60 (15.5)	.22
Hip or knee osteoarthritis, n (%)	156 (20.6)	33 (19.1)	43 (21.8)	80 (20.7)	.81
Medication use					
Aspirin, n (%)	586 (77.5)	137 (79.2)	149 (75.6)	300 (77.7)	.71
Statins, n (%)	616 (81.5)	145 (83.8)	164 (83.2)	307 (79.5)	.37
Beta blocker, n (%)	315 (41.7)	79 (45.7)	72 (36.5)	164 (42.5)	.19
Diuretics, n (%)	190 (25.1)	**57 (32.9)**	**50 (25.4)**	**83 (21.5)**	**.016**
ACE inhibitor, n (%)	234 (31.0)	**68 (39.3)**	**62 (31.5)**	**104 (26.9)**	**.014**
Calcium antagonist, n (%)	167 (22.1)	45 (26.0)	47 (23.9)	75 (19.4)	.18

	Total sample (n=756)	≥3 lesions (n=173)	2 lesions (n=197)	1 lesion (n=386)	P-value
Table 1 (Continued)					
Nitroglycerin, n (%)	67 (8.9)	**25 (14.5)**	**16 (8.1)**	**26 (6.7)**	**.011**
Anticoagulants, n (%)	125 (16.5)	**40 (23.1)**	**30 (15.2)**	**55 (14.2)**	**.028**
Digoxin, n (%)	18 (2.4)	**9 (5.2)**	**3 (1.5)**	**6 (1.6)**	**.042**
Antiarrhythmics, n (%)	21 (2.8)	8 (4.6)	4 (2.0)	9 (2.3)	.27
Anti-depressives, n (%)	45 (6.0)	**13 (7.5)**	**3 (1.5)**	**29 (7.5)**	**.009**
Anxiolytics, n (%)	31 (4.1)	9 (5.2)	4 (2.0)	18 (4.7)	.22
Hypnotics, n (%)	34 (4.5)	**16 (9.2)**	**3 (1.5)**	**15 (3.9)**	**.001**
Anatomical lesion location					**<.001**
Non-significant lesion, n (%)	71 (9.4)	**0 (0.0)**	**0 (0.0)**	**71 (19.2)**	
Proximal lesions, n (%)	219 (29.0)	**31 (19.3)**	**69 (36.7)**	**119 (32.2)**	
Distal lesions, n (%)	363 (48.0)	**89 (55.3)**	**94 (50.0)**	**180 (48.6)**	
Proximal and distal lesions, n (%)	66 (8.7)	**14 (25.5)**	**25 (13.3)**	**0 (0.0)**	
Vascular laboratory assessment					
PFWD, median (IQR), m	80 (40-130)	70 (40-130)	80 (50-140.0)	70 (30-130)	.69
MWD, median (IQR), m	250 (140-500)	**230 (120-400)**	**250 (140-520)**	**280 (160-500)**	**.028**

	Total sample (n=756)	≥3 lesions (n=173)	2 lesions (n=197)	1 lesion (n=386)	P-value
Table 1 (Continued)					
Ankle-brachial index					
Resting, median % (IQR)	65.0 (53.0-79.0)	**55.5 (48.0-67.0)**	**64.0 (53.0-75.0)**	**71.0 (59.0-83.0)**	**<.001**
Post-exercise, median % (IQR)	35.0 (26.0-54.0)	**28.0 (20.0-39.0)**	**32.0 (25.0-46.0)**	**41.0 (30.0-62.0)**	**<.001**

Abbreviations: ABI = ankle-brachial index, ACE = angiotensin-converting enzyme, CABG = coronary artery bypass graft, COPD = chronic obstructive pulmonary disease, IQR = interquartile range, MWD = maximum walking distance, PCI = percutaneous coronary intervention, PFWD = pain free walking distance, SD = standard deviation, TIA = transient ischemic attack.

Table 2 – Total number of events by event category for the total sample and stratified by extensiveness of lesions.

Event category	Total sample (n=756)	≥3 lesions (n=173)	2 lesions (n=197)	1 lesion (n=386)
Amputation (%)	10 (1.3)	5 (2.9)	2 (1.0)	3 (0.8)
Unstable angina (%)	36 (4.8)	8 (4.6)	11 (5.6)	17 (4.4)
Myocardial infarction (%)	37 (4.9)	14 (8.1)	5 (2.5)	18 (4.7)
Heart failure (%)	28 (3.7)	10 (5.8)	7 (3.6)	11 (2.8)
CVA/TIA (%)	47 (6.3)	12 (6.9)	17 (8.6)	18 (4.7)
Death (%)	87 (11.5)	33 (19.1)	18 (9.1)	36 (9.3)

Abbreviations: CVA=cerebrovascular accident, TIA = transient ischemic attack.

Time-to-first event analysis

Figure 1 presents the cumulative incidence over time for experiencing a first adverse event, illustrating that the cumulative incidence was higher for patients presenting with ≥3 lesions (log-rank test P<.001). Results from the time-to-first event Cox regression analysis indicated that patients presenting with ≥3 lesions were more likely to experience a first adverse event during 3.2 year follow-up as compared with those presenting with 1 lesion in the unadjusted model (unadjusted HR=1.93, 95%CI 1.37-2.72, P=.0002). No increased risk of experiencing a first adverse event was observed among patients presenting with 2 lesions vs. those having 1 lesion (unadjusted HR=0.99, 95%CI 0.67-1.46, P=.96).

Results from the multivariable time-to-first event analysis are listed in Table 3; the presence of ≥3 lesions (HR=1.56, 95%CI 1.09-2.25, P=.016) remained an independent predictor of experiencing an adverse event. Other significant covariates included age (HR=1.03, 95%CI 1.01-1.05, P=<.001), prior angina (HR=1.68, 95%CI 1.11-2.54, P=.014), prior MI (HR=1.51, 95%CI 1.03-2.23, P=.035) and COPD (HR=1.87, 95%CI 1.32-2.66, P=<.001). The c-index for the multivariable model was 0.68.

Sensitivity analyses

A total of 45 (6%) patients experienced more than one adverse event over time; sensitivity analyses - as opposed to the main time-to-first event analyses - were performed to calculate the cumulative 3.2 year risk of experiencing *multiple* adverse events by extensiveness of the disease (≥3 , 2 vs. 1 lesions [reference]) using an unadjusted and multivariable adjusted Cox-based intensity-elapsed time model. The mean cumulative incidence of *multiple* adverse events by the number of lesions was significantly higher for patients with ≥3 lesions (log-rank test P=.0002, Appendix 2). Apart from their risk of experiencing a first adverse event, having ≥3 lesions (HR=1.66, 95%CI 1.21-2.28, P=.001) was also associated with an increased cumulative risk of experiencing more than one adverse event during the 3.2 years of follow-up. Other relevant indicators of an increased cumulative risk were age, prior MI, COPD, heart failure, and smoking. Full model results are presented in Appendix 3.

Figure 1 – The cumulative incidence of a first adverse event by extensiveness of lesions (≥ 3 or 2 vs. 1 lesions [reference]) during a median follow-up of 3.2-years.

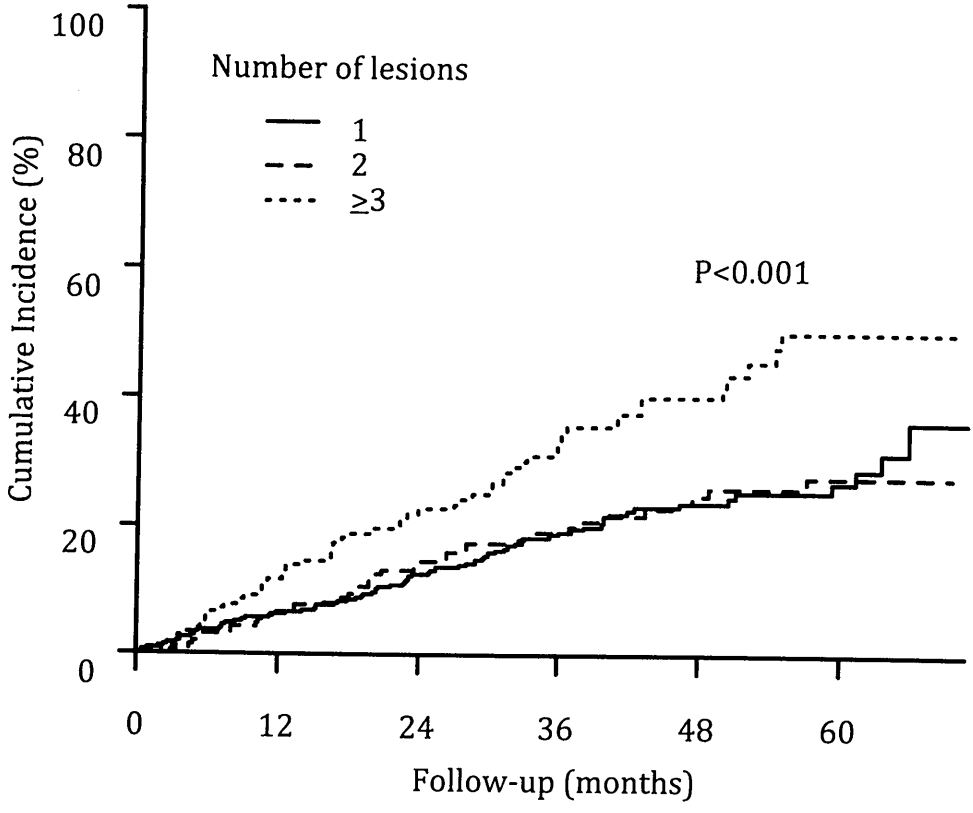


Table 3 – The association between 3.2-year first adverse event risk and extensiveness of lesions.

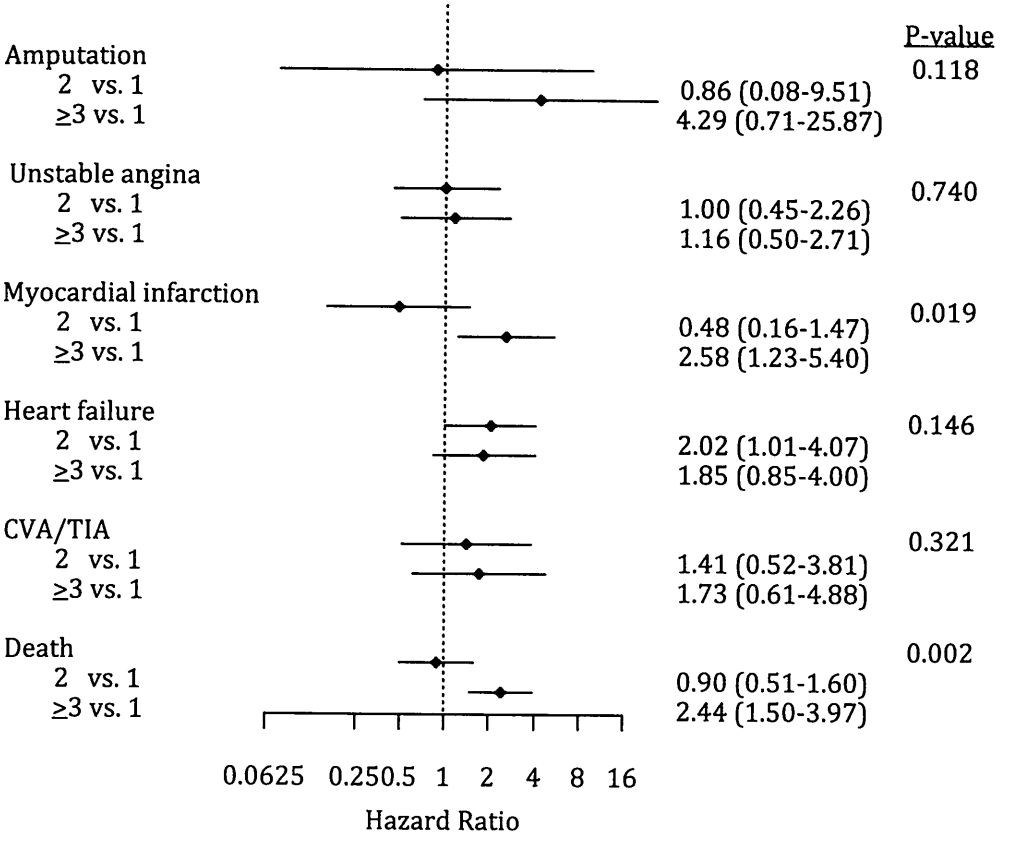
	HR	95%CI	P-value
Age	**1.03**	**1.01-1.05**	**<.001**
Female	1.12	0.82-1.55	.47
Body mass index	1.00	0.96-1.03	.86
Prior angina	**1.68**	**1.11-2.54**	**.014**
Prior myocardial infarction	**1.51**	**1.03-2.23**	**.035**
Heart failure	1.58	0.91-2.76	.11
Prior coronary artery bypass graft	0.79	0.48-1.29	.34
Prior percutaneous coronary intervention	1.21	0.74-1.98	.46
Prior stroke	1.00	0.55-1.83	.99
Prior transient ischemic attack	0.92	0.53-1.59	.76
Chronic obstructive pulmonary disease	**1.87**	**1.32-2.66**	**<.001**
Hypertension	1.08	0.76-1.53	.68
Dyslipidemia	1.31	0.92-1.87	.14
Diabetes mellitus	1.17	0.81-1.70	.40
Renal dysfunction	1.32	0.84-2.09	.23
Smoking	1.40	0.99-1.98	.06
Proximal lesion	1.00	0.71-1.42	.99
Number of lesions			
2 vs. 1	0.98	0.66-1.46	.93
3+ vs. 1	**1.56**	**1.09-2.25**	**.016**

Abbreviations: CI=confidence interval, HR=hazard ratio.

Event-specific analyses

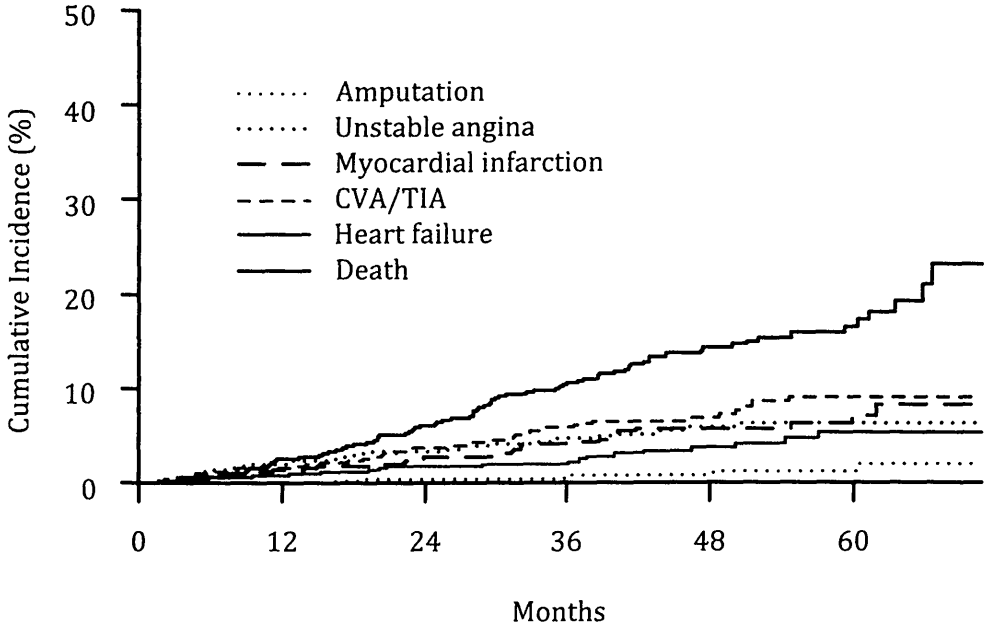
Results from the multivariate Cox regression analysis stratified by event type demonstrated that MI (HR=2.58, 95%CI 1.23-5.40, P=.019) and death (HR=2.44, 95%CI 1.50-3.97, P=.002) were the events that were more likely to occur in patients presenting with ≥3 lesions as compared with those having 1 lesion (Figures 2-3). However, due to the low number of individual event types, the interaction between number of lesions and event type was not significant (P=.25).

Figure 2 – The association between the extensiveness of lesions (≥ 3 or 2 vs. 1 lesions [reference]) and first adverse event risk and, stratified by event type. The Hazard Ratios (HR) and 95% Confidence Intervals (CI) are depicted for lower-extremity amputation, unstable angina, myocardial infarction, heart failure, stroke/transient ischemic attack, and mortality. *Significant (P<.05).



Abbreviations: CVA = cerebrovascular accident (stroke), TIA = transient ischemic attack.

Figure 3 - The cumulative incidence of experiencing adverse events stratified by event type (lower-extremity amputation, unstable angina, myocardial infarction, heart failure, stroke/transient ischemic attack, and mortality) during a median follow-up of 3.2-years.



Abbreviations: CVA = cerebrovascular accident (stroke), TIA = transient ischemic attack.

DISCUSSION

This study provides further insight into strategies that can help risk-stratify patients with a new diagnosis of PAD (Rutherford Grade I) based on a simple comparison by the number of arterial lesions within the lower-extremity arteries identified at presentation. In addition, this is the first study, of which we are aware, to also estimate PAD patients' risks of experiencing *multiple* adverse events over time using novel multiple event modeling techniques. In a vascular specialty setting, we found that half of our patients presented with 1 lesion, whereas a quarter had ≥3 lesions upon diagnosis. At least 1 adverse event was observed in a quarter of the population and only a minority (6%) experienced ≥2 events during the 3-year study follow-up. Having more extensive lesions (≥3) was not only predictive of an increased risk of experiencing a *first* adverse event as assessed by a traditional time-to-first event Cox regression model, but was also associated with experiencing *multiple* events over time as compared with patients presenting with an isolated lesion as modeled with a Cox-based intensity-elapsed time model. Additionally, the results remained consistent throughout our analyses, while adjusting for known traditional PAD risk factors.

While it seems obvious to assume that patients with multiple lower-extremity arterial lesions have a poorer prognosis as compared with those having a single lower-extremity lesion, prior studies only demonstrated that patients with PAD and concomitant coronary or carotid disease (i.e., having several arterial beds affected) have increased risks of experiencing adverse events as compared with those having a single arterial bed affected.[3,5] These studies were unable to perform comparisons by the number of lesions *within* one arterial bed for patients with PAD, i.e., comparisons for lesions within patients' lower-extremity arteries.[3-5] There was only 1 study of 224 younger, non diabetic patients recruited in 1985 that demonstrated that patients with multiple lower-extremity arterial lesions - as verified by combining information derived from segmental blood pressure measurements and Doppler evaluation of velocity and flow - had lower 6-year survival rates as compared with patients having a single lesion.[10]

Due to its many limitations, including a non-diabetic population that is not representative of the PAD population, lack of visualization of arterial segments, and limited sample size, this aged study precluded any firm conclusions about the prognostic association of extensiveness of lower-extremity PAD with outcomes. We had a unique chance to address this question in a larger cohort of patients in which adverse risk factors were proportionally represented in accordance with their prevalence in a real-world clinical setting.[3, 5] Lesions were uniformly documented with modern duplex ultrasound techniques upon diagnosis. Detailed and complete follow-up information was available for the first event as well as multiple events thereafter. Having incorporated this information on multiple events into our state-of-the-art analytic models, our study has the potential to significantly advance our understanding of different subpopulations of patients with PAD, and to better inform patients and their clinicians about expected outcomes.

Our study results seem to suggest that the risk of experiencing adverse events may increase along with the number of lower-extremity lesions. This raises the question whether it is possible that the manifestation of atherosclerosis may present differentially among individuals' arteries. A more aggressive expression of atherosclerosis has been found in patients' with distal disease vs. aortoiliac disease and in patients in whom higher inflammation markers can be found.[14, 15] These studies only suggest what concomitant factors are associated with a more aggressive underlying atherosclerotic process, but were unable to document whether this can be linked to patients' lesion extensiveness and their subsequent outcomes.[14, 15] Therefore, future work needs to verify whether presenting with more extensive lower-extremity lesions is associated with a more aggressive underlying atherosclerotic process as expressed by higher inflammation markers or undergoing multiple lower-extremity revascularizations, in order to better characterize PAD subpopulations that are at increased risk of an adverse prognosis.

Apart from investigating the potential pathophysiological underpinnings for the adverse prognosis associated with having more extensive lower-extremity lesions, it seems a logical next step to verify whether stratifying patients by the number of lower-extremity lesions upon diagnosis – using various diagnostic instruments (e.g., angiography, duplex ultrasound testing, or segmental blood pressure measurements) – will be a practical and useful risk stratification tool in routine clinical care. Our results indicate that information on the number of lesions adds to the prognostic information derived from traditional PAD risk factors that we were able to adjust for in our models. Future studies will need to evaluate whether implementing quality of care protocols specifically directed to the subgroups of patients presenting with multiple lesions (e.g., closer monitoring of patients by organizing more frequent follow-up visits in combination with aggressive adverse risk management, and more pro-active screening for coronary or cerebrovascular disease), may actually be able to curb the adverse risk observed in patients with PAD presenting with multiple lesions.

Other areas to focus on by both clinicians and researchers in the field of PAD are ways in which we can more accurately predict patients' overall risk of experiencing future events following a diagnosis of PAD. In the current study, we performed state-of-the-art analyses to assess patients' risk of experiencing multiple events over time.[13] Patients with more extensive lesions not only seem to be at risk of experiencing a first adverse event, but were also at risk of experiencing multiple events. While we did not observe a great amount of multiple adverse events during the limited 3-year study follow-up, applying these techniques seem even more relevant when investigating longer-term outcomes and the need to have recurrent procedures in this vulnerable group of patients. Assessing patients' true cumulative risk of having multiple adverse events over time becomes more standard within cardiovascular research,[16, 17] but has rarely been applied for research investigating PAD populations.

Our results should be interpreted in the context of the following potential limitations. Not all arterial segments were visualized because duplex ultrasound testing was guided by clinical evaluation as performed by vascular surgeons. There are no studies available addressing the correspondence between patients' self-reported leg symptoms discussed during their initial evaluation by a vascular specialist, suspected lesion information derived from the physical examination, and the true number of lesions identified by duplex ultrasound testing. However, chances that lesions were missed are minimal because duplex ultrasound testing was performed by a systematic approach (i.e., segments were additionally visualized if a lesion elsewhere was expected due to flow disturbances). Next, to maximize our power, we explored patients' risk of adverse events by use of a composite endpoint, but we additionally explored patients' risk by event type using a hierarchical analysis. Also, because patients were recruited from 2 vascular surgery outpatient clinics, our results may not be necessarily generalizable to patients with PAD seen in other settings. And finally, since this was an observational study, we cannot rule out the possibility of residual confounding, despite being able to adjust for clinically important factors.

CONCLUSIONS

This study demonstrates that patients with PAD presenting with more lower-extremity arterial lesions upon diagnosis are at increased risk of experiencing a first as well as multiple, major adverse cardiovascular events over time as compared with those having only 1 or 2 lower-extremity lesions. Comparing PAD outcomes as a function of patients' number of lower-extremity lesions may offer a new paradigm that may serve clinicians to better determine patients' risk for an adverse prognosis at initial PAD diagnosis, and that may open up new possibilities to develop and evaluate care innovations specifically directed towards patients that present with $\geq$3 lesions within their lower-extremity arteries, possibly representing a phenotype that is associated with a more aggressive form of atherosclerotic disease.

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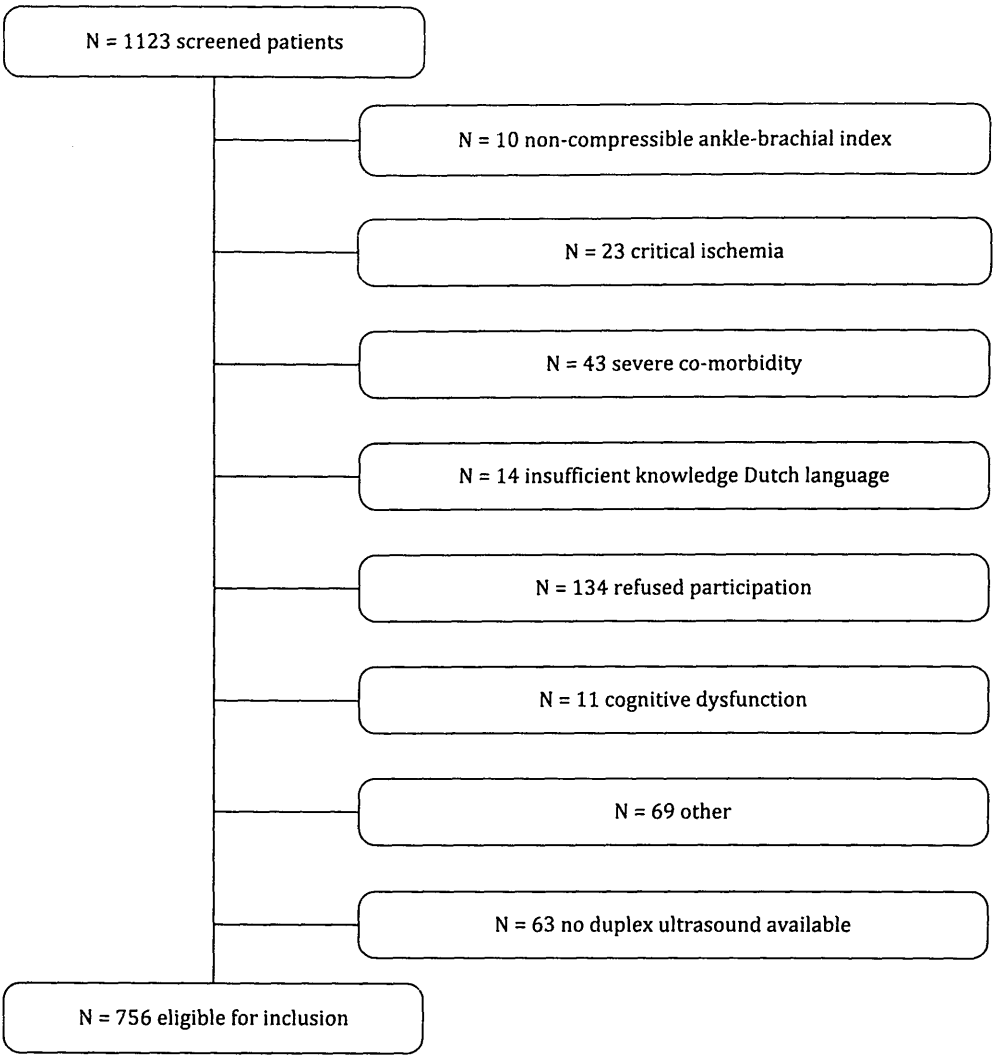
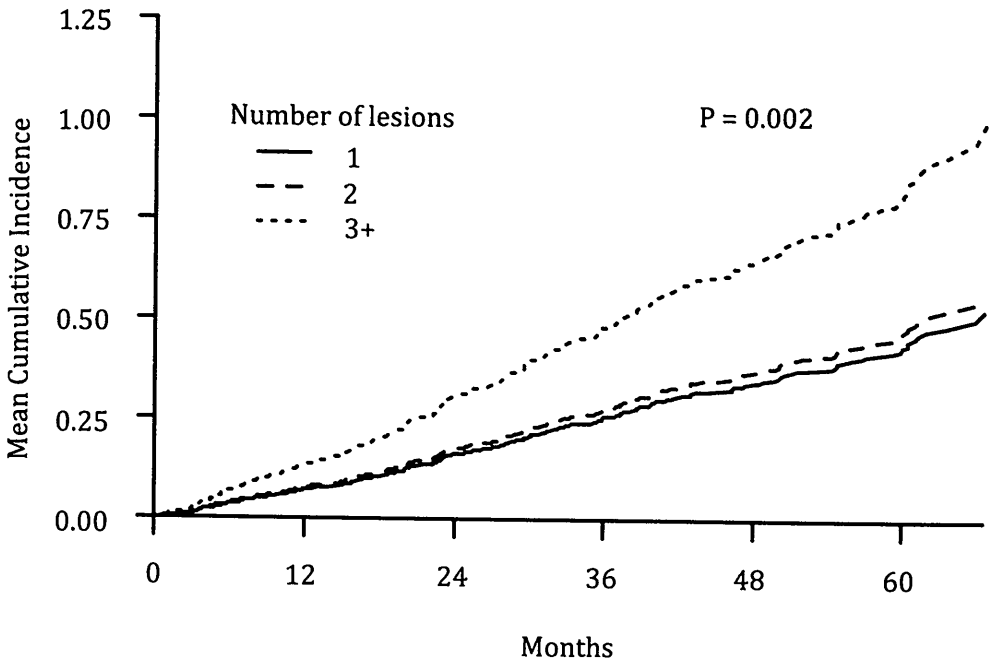
APPENDIX 1 – Flow chart of the study population.



APPENDIX 2 – The mean cumulative incidence for experiencing multiple adverse events by extensiveness of lesions during a median follow-up of 3.2-years.

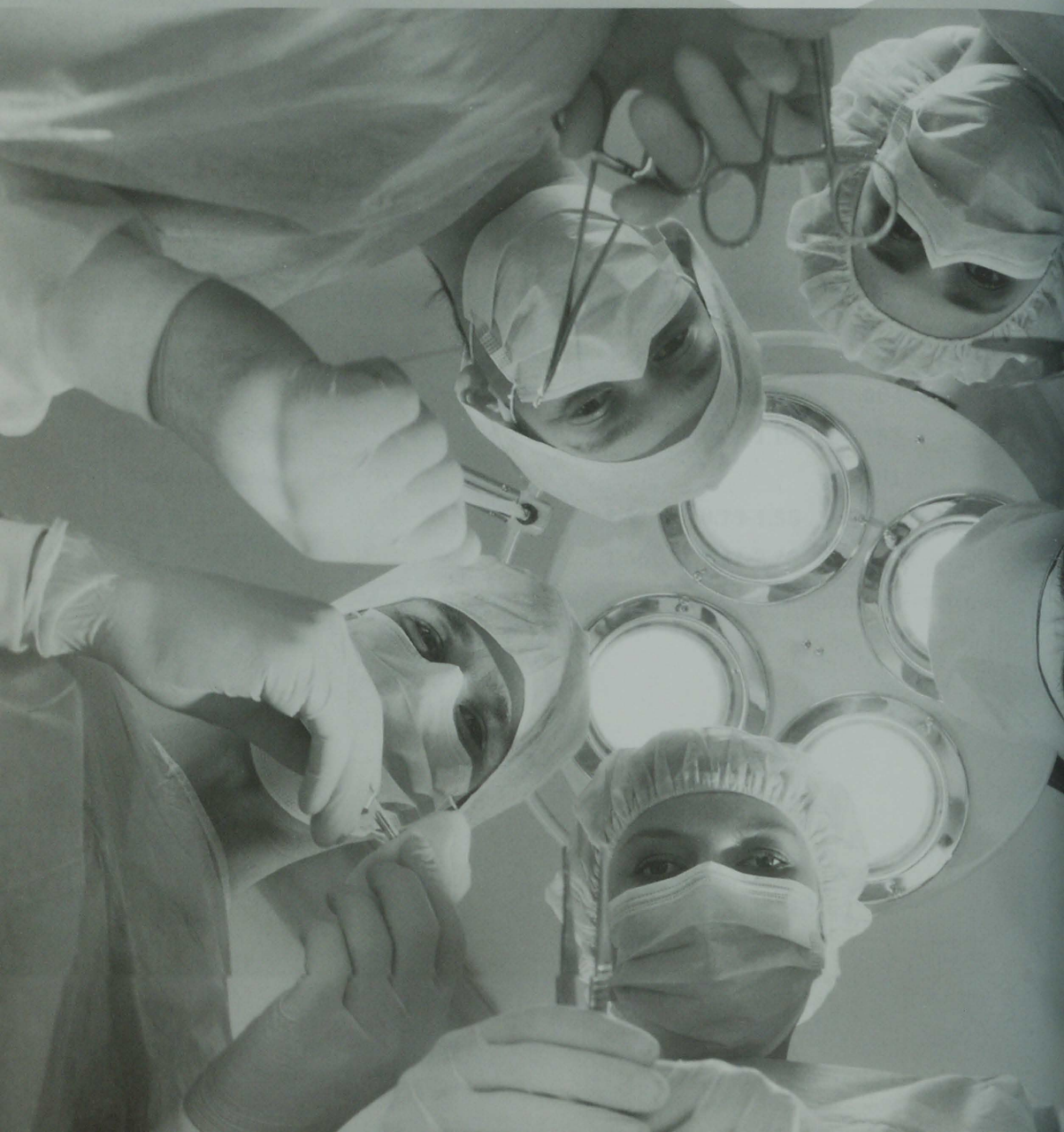


APPENDIX 3 - The association between 3.2-year multiple adverse events risk and extensiveness of lesions.

	HR	95%CI	P-value
Age (per +10 years)	**1.36**	**1.17-1.59**	**<.001**
Female	1.15	0.88-1.51	.496
Body mass index (per +5 kg/m^2)	1.03	0.89-1.21	.519
Prior angina	1.31	0.92-1.87	.189
Prior myocardial infarction	**1.44**	**1.04-1.99**	**.045**
Heart failure	**1.77**	**1.07-2.91**	**.023**
Prior coronary artery bypass graft	1.02	0.69-1.51	.967
Prior percutaneous coronary intervention	1.22	0.81-1.86	.264
Prior stroke	1.13	0.69-1.86	.777
Prior transient ischemic attack	0.69	0.43-1.13	.209
Chronic obstructive pulmonary disease	**1.74**	**1.27-2.38**	**.001**
Hypertension	1.00	0.74-1.35	.989
Dyslipidemia	1.30	0.95-1.77	.149
Diabetes mellitus	1.21	0.89-1.65	.222
Renal dysfunction	1.18	0.79-1.75	.587
Smoking	**1.51**	**1.13-2.03**	**.004**
Proximal lesion	0.86	0.63-1.16	.157
Number of lesions			**.001**
2 vs. 1	**1.11**	**0.79-1.55**	
3+ vs. 1	**1.66**	**1.21-2.28**	

Abbreviations: CI=confidence interval, HR=hazard ratio, kg=kilogram, m^2=square meters.

Chapter 5



One-year health status

benefits following invasive treatment for lower-extremity peripheral arterial disease

the importance of patients' baseline health status

5

M. van Zitteren, J. Denollet, J.M. Heyligers, J.W. Elshof, M.J. Nooren, D.H. Burger, W.M. de Fijter, M.K. Dinkelman, P.W. Vriens, K.G. Smolderen. One-year health status benefits following invasive treatment for lower-extremity peripheral arterial disease: the importance of patients' baseline health status. *Manuscript in preparation for submission (abstract presentation at Quality of Care and Outcomes Research 2012, and the Scientific Sessions 2012 of the American Heart Association).*

ABSTRACT

Background: Limited information is available on health status gains to be expected following invasive treatment. We compared 1-year health status outcomes by invasive treatment referral among patients with PAD and evaluated whether baseline health status was indicative of 1-year health status gains.

Methods and results: Baseline and 1-year health status (SF-12, Physical Component Score [PCS]) was assessed in 474 patients with newly diagnosed PAD (Rutherford Grade I) enrolled from 2 Dutch vascular clinics (March 2006-August 2011). One-year treatment strategy (invasive vs. non-invasive) and clinical information was abstracted. Quartiles of baseline health status scores and mean 1-year health status change scores were compared as a function of invasive treatment. The numbers needed to treat (NNT) to obtain clinically relevant changes in 1-year health status were calculated. A propensity weight adjusted linear regression analysis was constructed to predict 1-year PCS scores. Invasive treatment was performed in 39%. Patients with baseline health status scores in the lowest quartile undergoing invasive treatment had the greatest improvement (11.3±10.3 vs. 5.3±8.5, P=.001, NNT=3), whereas those in the highest quartile did not substantially improve (0.8±6.3 vs. -3.0±8.2, P=.025, NNT=90). One-year invasive treatment (B=2.39, 95%CI 0.04;4.73, P=.046) and lower baseline health status scores (B=-0.52, 95%CI -0.64;-0.41, P<.0001) were independently associated with greater 1-year health status gains.

Conclusions: We found substantial improvements in patients with lower starting levels of their health status, whereas patients with higher starting levels had less to gain. Whether this implies that only patients below certain health status thresholds should be offered invasive treatment needs to be determined.

INTRODUCTION

The primary goal of treatment in symptomatic lower-extremity peripheral arterial disease (PAD) is to alleviate patients' symptoms and to improve their health status.[1-5] Despite this objective, patients' health status may not always be a decisive factor in referring patients to invasive treatment.[6] In addition, in large clinical trials, outcomes of interest are often focused on hemodynamic success rates,[7-9] as opposed to clinically meaningful improvements in patients' health status.

It is unclear whether invasive treatment is being applied in those patients for whom the greatest health status benefit can be expected. One of the factors that may predict health status outcomes following invasive treatment is pre-procedural health status, according to prior work in patients undergoing percutaneous coronary intervention. This work potentially suggests that patients with lower health status scores have the most to gain from an invasive treatment vs. those who have high pre-procedural health status scores.[10] This has never been evaluated in PAD. It is unknown whether invasive treatments are being offered to patients with PAD across the whole spectrum of pre-procedural health status scores in daily clinical practice.

Given these gaps in knowledge and given the rapid increase in use of endovascular procedures and its associated costs over the past years,[11-13] it seems desirable to be able to quantify and predict expected health status benefits by treatment strategy based on pre-procedural, measurable characteristics such as patients' health status. Therefore, the present study aimed to document the invasive treatment rates as a function of patients' pre-procedural health status, and quantify the magnitude of 1-year benefits in patients' self-reported health status across the range of pre-procedural health status scores, thereby comparing health status benefits for patients with PAD who were treated invasively vs. non-invasively. Identifying which patients will benefit most from invasive treatment based on pre-procedural information will be extremely helpful to both patients and clinicians as it will facilitate informed decisions on invasive PAD strategies thereby weighing information on expected gains and potential risks linked to these invasive procedures.

METHODS

Study population and design

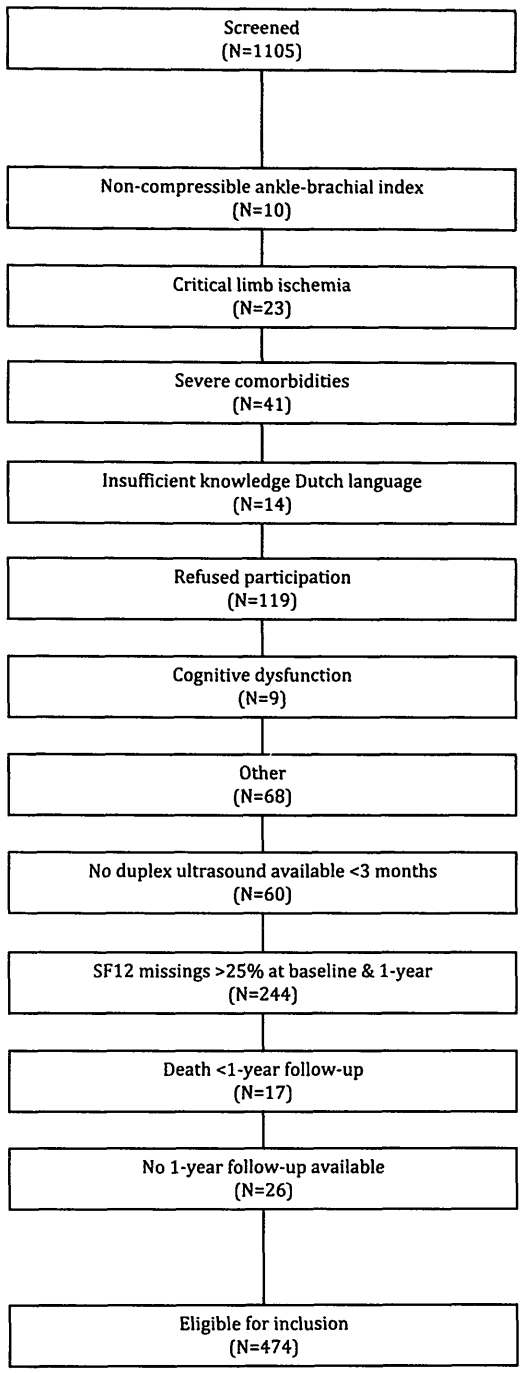
A total of 474 consecutive patients with new onset symptoms of PAD or exacerbation of existing PAD symptoms requiring treatment were enrolled in this study (Figure 1). This study had a prospective observational design for which patients were consecutively enrolled at 2 vascular surgery outpatient clinics (St. Elisabeth Hospital and TweeSteden Hospital, Tilburg, the Netherlands) (March 2006 - August 2011). Patients were eligible for inclusion if their ankle-brachial index (ABI) was abnormal at rest (ABI $\leq$0.90) or decreased post-exercise following a distance-limited (1000 meters) treadmill walking protocol (decrease $\geq$15% from the resting ABI). Exclusion criteria were a non-compressible ABI ($\geq$1.30), critical limb ischemia, severe cognitive impairment or severe somatic or psychiatric comorbidities (e.g., active cancer treatment or psychosis), insufficient knowledge of the Dutch language, or other reasons (e.g., participation in another study, treatment for PAD started before inclusion in the present study). Because this study specifically focused on 1-year change in physical health status and anatomical lesion location, patients were additionally excluded if: (1) patients had >25% missing values on their health status assessments; (2) patients died during the first year of follow-up, or if (3) no pre-procedural duplex ultrasound examination was available in patients' medical charts within 3 months prior to or after inclusion.

All patients underwent a vascular diagnostic work-up upon enrollment including a clinical evaluation (i.e., thorough-history taking and physical examination) by the treating vascular surgeon and vascular laboratory assessments (i.e., ABI assessments at rest and post-exercise as well as clinician-guided duplex ultrasound examinations). A patient interview and self-report questionnaires were completed upon enrollment (i.e. prior to being referred for their primary treatment) and after 1-year follow-up to document patients' sociodemographics, their self-reported physical health status, and psychological factors. Information on baseline medication use, cardiovascular history and clinical factors was retrieved through medical chart abstraction upon enrollment.

Finally, patients' medical records were searched to collect information on primary treatment strategies administered during the 1-year follow-up period (i.e., invasive vs. non invasive strategies).

The local ethics committee of each participating institution approved the study that was designed in line with the Helsinki Declaration and all participants provided written informed consent. Study participation did not influence the type of treatment patients would receive because the study was observational in nature.

Figure 1 – Overview of the study population.



MEASURES

Assessment of health status

The Dutch version of the 12-item Short Form 12 (SF-12), a generic health status instrument that has been widely applied in cardiovascular populations,[2, 14] was used to assess patients' self-reported pre-procedural (i.e., prior to treatment) and 1-year physical health status (Physical Component Summary [PCS] Score). PCS scores (range between 0-100, mean score=50, SD=10) were standardized against the Dutch general population norms.[15] Higher scores were indicative of better physical functioning.[15] Based on what ranges of scores to expect following invasive treatment in PAD in similar populations, [4, 16-18] we calculated clinically relevant changes based on a 1-year change score (1-year health status score minus pre-procedural health status score) falling within the range of 0.5 SD (≥5 points) and 1.0 SD (≥10 points).

One-year treatment strategies

Patients' medical records were searched 1-year following PAD diagnosis to document information on the type of treatment patients had received since enrollment at the vascular specialty clinics.[6] A variety of treatment strategies were available at both enrolling centers including non-invasive strategies such as a formal supervised exercise therapy program that is supported by a regional network of certified physiotherapists who are specifically trained to provide specific supervised exercise programs for PAD; smoking-cessation counseling; and pharmacotherapy (e.g., aspirin, anticoagulants, and statins).[6] Two primary treatment categories were discriminated for analytic purposes: If no hospital admissions for vascular reasons were documented within the first year following diagnosis, patients were considered to have had *non-invasive treatment* options only. Patients were assigned to the *invasive treatment* category if any invasive lower-extremity procedure (lower-extremity revascularization [percutaneous transluminal angioplasty; PTA with or without stent], endarterectomy, or bypass surgery) was documented in their medical records.[6]

Disease severity

A handheld Doppler instrument (Imexlab 9000; Imex Medical Systems Inc, Golden Colorado) was used by trained vascular technicians to confirm PAD diagnosis by measuring patients' resting ABI and post-exercise ABI following a distance-limited (1000 meters) treadmill test. In addition, patients' pain-free walking distance was also assessed. In general, the ABI is calculated by dividing the highest systolic ankle pressure in each leg (posterior tibial artery or dorsalis pedis artery) by the highest systolic brachial pressure. A resting ABI of $\leq$0.90[19, 20] or a post-exercise ABI decrease of $\geq$15% as compared with the resting ABI is considered to be abnormal and indicative for PAD.[3] The lowest ABI at rest or post-exercise was used in the analyses.

Duplex ultrasound examination protocol

A duplex ultrasound examination of the lower-extremities was ordered by the treating vascular surgeon based on their clinical evaluation as part of the diagnostic work-up. Trained vascular technicians performed the duplex ultrasounds using the Toshiba Xario ultrasound system (Xario XG; Toshiba Medical Systems Europe, Zoetermeer, the Netherlands) from which lesion information was derived (i.e., anatomical lesion location, the number of lesions and lesion severity). Severity of lesions was measured by the peak systolic velocity (PSV [cm/sec]) ratio. Lesions with a PSV ratio $\geq$2.5, or total occlusions (no flow, and no PSV ratio could be measured) were considered significant. Lesions were scored as proximal or distal lesions only, having both and distal lesions, or having non-significant lesions. Duplex ultrasounds were read by a team of 3 physicians (surgical fellow and 2 vascular surgeons) prior to the study's analyses to categorize the anatomical lesion location of the lesions that patients presented with upon enrollment.[21] A detailed description of the duplex ultrasound protocol has been published elsewhere.[21]

Clinical risk factors

Information on clinical risk factors was abstracted from patients' medical records and included: cardiac history (angina, myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, congestive heart failure), cerebrovascular history (stroke, transient ischemic attack), current smoking, diabetes mellitus, dyslipidemia, hypertension, body mass index (BMI, kg/m^2), chronic obstructive pulmonary disease (COPD), renal dysfunction, back pain, and knee or hip osteoarthritis. In addition, patients' medication use following their vascular diagnostic evaluation was abstracted from their medical records including the following categories: aspirin, statins, beta blockers, diuretics, angiontensin-converting enzyme (ACE) inhibitors, calcium antagonists, nitroglycerin, anti-coagulants, digoxin, anti-arrhythmics, anti-depressants, anxiolytics, and hypnotics.

Sociodemographic and psychological factors

Patients' age and sex was documented through medical chart abstraction. Information on sociodemographic factors was derived from purpose-designed self-report questionnaires that patients completed upon enrollment and included: marital status (no partner vs. partner), educational background (<high school education vs. ≥high school education), and work status (non-active vs. active work status). In addition, the presence of clinically relevant depression and anxiety was assessed by the Hospital Anxiety and Depression Scale (HADS), using cut-off scores ≥8 on both the anxiety and depression subscale.[22] Finally, the DS14, an instrument that measures the joint tendency of social inhibition and negative affect, was used to assess the presence of a distressed (Type D) personality.[23] Cut-off scores ≥10 on both the social inhibition and negative affectivity subscales denotes a Type D personality.[23]

Statistical analysis

Patients' baseline characteristics as well as 1-year PCS (health status; Physical Component Score) change scores were described for the total population and compared by quartiles of pre-procedural PCS scores. The Chi-square test, One-way ANOVA (Analysis of Variance) and the Kruskal Wallis test were used for descriptive purposes, as appropriate.

To quantify the magnitude of the health status change effects at 1-year following treatment referral, effect sizes (Cohen's D) were calculated for patients who underwent invasive vs. non-invasive treatment by quartiles of their pre-procedural PCS scores. A Cohen's D of 0.2, 0.5, and 0.8 were considered as a small, medium, and large effect, respectively. Similarly, the number needed to treat (NNT) to obtain a clinically relevant improvement in physical health status falling within the range of 0.5 SD (≥5 points) and 1.0 SD (≥10 points) was calculated for quartiles of pre-procedural PCS scores. The NNT is widely used to translate risk measures into clinical and statistical significance to guide physicians, policy makers and patients through the clinical decision making process.[24-26] The NNT is defined as the number of persons needed to treat to prevent 1 outcome and is calculated by the inverse of the absolute risk reduction.[24, 25] For example, if NNT=10, then 10 patients need to be treated to prevent 1 outcome. The smaller the number, the more efficient the treatment strategy is.[27]

Since the study was observational in nature, propensity weights were calculated for all patients based on all baseline characteristics for the propensity to undergo invasive vs. non-invasive treatment. A propensity-adjusted linear regression model was constructed to examine the association between treatment strategy (invasive vs. non-invasive), pre-procedural health status and 1-year PCS change scores (dependent variable: 1-year PCS score minus pre-procedural PCS score).

The model was sequentially built by the following steps: (1) treatment strategy (invasive vs. non-invasive), pre-procedural PCS scores, and the interaction between treatment strategy and pre-procedural PCS scores; (2) demographics (age, sex), hospital site, marital status (partner vs. no partner), educational background (≥high school education vs. <high school education); (3) anatomical lesion location (proximal lesions only, distal lesions only, both proximal and distal lesion, or non-significant lesions), 1-year change in resting ABI (1-year ABI at rest minus pre-procedural ABI at rest); (4) cardiac history, cerebrovascular history, current smoking, diabetes mellitus, BMI, renal dysfunction, COPD, back pain and hip or knee osteoarthritis; and (5) depression. Finally, the explained variance (R^2) was calculated for all individual variables included in the model.

Missing SF-12 items were handled by multiple imputation (mean of 5 iterations) if ≥75% of all items were completed. Missing items were assumed to be missing at random. A total of 16 patients had >25% missing values at both baseline and 1-year follow-up. Compared with the 474 included patients, those 16 who were not in the analyses were slightly older (P=.005, Cohen's D=0.8) and more likely to use anticoagulants (P=.040, Cramér's V=0.099). They were similar in terms of all other characteristics. A sensitivity analysis was performed based on complete case analyses.

PASW Statistics 19.0 for Windows (SPSS inc. Chicago, IL) was used to execute all analyses. All tests were two-tailed and statistical significance was considered if P-values were <.05.

RESULTS

Baseline characteristics

Table 1 presents patient characteristics for the total sample (n=474) and stratified by quartiles of self-reported pre-procedural health status scores. The cohort's mean age was 65.0 years (±9.4 years) and 67% was male.

Patients with lower health status scores were more likely to have a lower educational status, a history of cardiovascular disease, other comorbidities or risk factors (such as a higher BMI, diabetes, COPD, and back pain), and to receive cardio protective medications and psychopharmaca as compared with patients having higher health status scores. While the ABI did not differ across health status categories, patients' with lower health status scores were more likely to have a shorter pain-free walking distance, to have undergone a prior lower-extremity surgical intervention, and to present with a proximal or non-significant lesion as compared with those with higher health status scores. Also, the presence of psychological comorbidities increased along with decreasing health status scores.

Physical health status scores by the receipt of 1-year invasive treatment

A total of 183 (39%) patients underwent invasive treatment ≤1 year following diagnosis, ranging from 41-46% in the lowest 3 health status quartiles to 24% in the highest quartile (P=.001).

When considering all patients' 1-year health status change scores by pre-procedural health status scores, a negative correlation between pre-procedural health status scores and change scores was observed for both patients receiving invasive (r=-0.38, 95%CI -0.50;-0.25, P<.0001), as well as non-invasive treatment (r=-0.39, 95%CI -0.50;-0.28, P<.0001) (Figure 2), suggesting that lower pre-procedural health status scores were associated with improvements in patients' health status at 1-year follow-up.

Table 1 - Baseline characteristics of the total sample and stratified by quartiles of baseline health status scores (physical component scores).

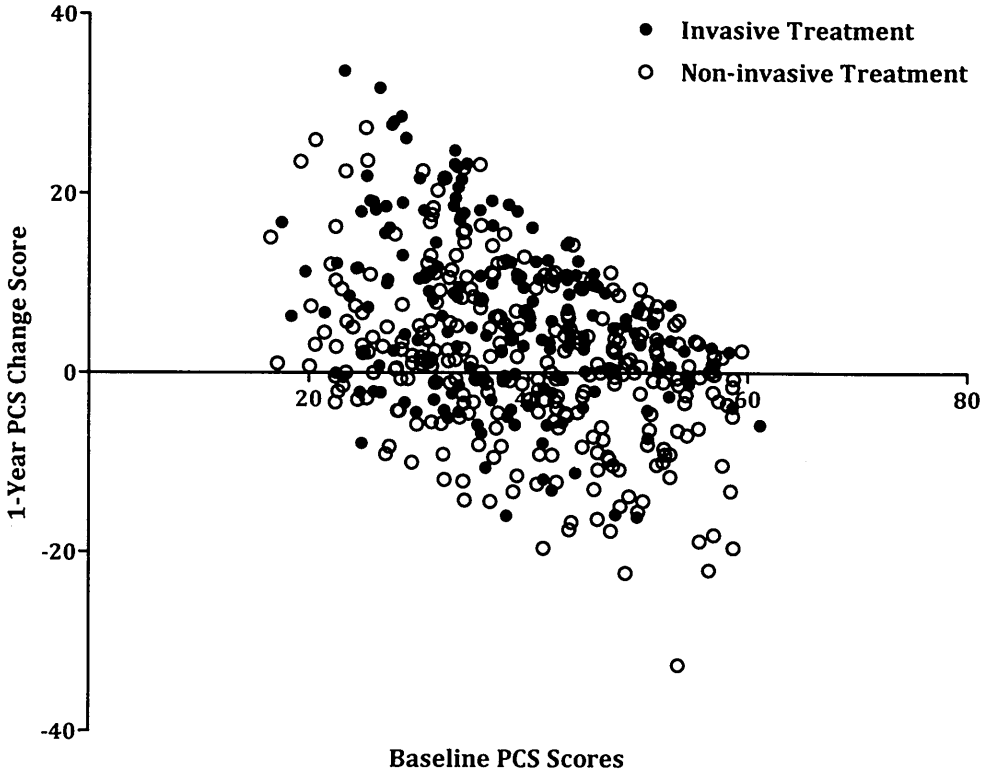
	Total sample (n = 474)	Quartile 1 (n = 119)	Quartile 2 (n = 118)	Quartile 3 (n = 119)	Quartile 4 (n = 118)	P-value
Demographics						
Age, mean (SD) years	65.0 (9.4)	63.8 (11.1)	65.3 (9.3)	65.1 (8.5)	65.8 (8.6)	.40
Male sex, n (%)	315 (66.5)	69 (58.0)	76 (64.4)	82 (68.9)	88 (74.6)	.06
Socioeconomic factors						
No partner, n (%)	112 (23.9)	33 (27.7)	29 (24.8)	26 (22.4)	24 (20.5)	.61
<High school education, n (%)	**116 (24.9)**	**39 (33.1)**	**33 (28.9)**	**23 (20.0)**	**21 (17.8)**	**.023**
Non-active work status, n (%)	335 (73.6)	88 (77.2)	84 (73.7)	87 (77.6)	76 (64.5)	.07
Cardiovascular history						
Angina pectoris, n (%)	65 (13.7)	16 (13.5)	19 (16.1)	17 (14.3)	13 (11.0)	.74
Myocardial infarction, n (%)	**87 (18.4)**	**22 (18.5)**	**28 (23.7)**	**25 (21.0)**	**12 (10.2)**	**.043**
CABG, n (%)	58 (12.2)	13 (10.9)	21 (17.8)	16 (13.5)	8 (6.8)	.07
PCI, n (%)	46 (9.7)	14 (11.8)	15 (12.7)	8 (6.7)	9 (7.6)	.25
Congestive heart failure, n (%)	21 (4.4)	8 (6.7)	8 (6.8)	3 (2.5)	2 (1.7)	.08
Stroke, n (%)	**39 (8.2)**	**10 (8.4)**	**15 (12.7)**	**11 (9.2)**	**3 (2.5)**	**.043**
TIA, n (%)	41 (8.7)	9 (7.6)	14 (11.9)	10 (8.4)	8 (6.8)	.55
Clinical factors						
Smoking, n (%)	220 (46.4)	59 (49.6)	48 (40.7)	50 (42.0)	63 (53.4)	.13
Diabetes mellitus, n (%)	**108 (22.8)**	**33 (27.7)**	**35 (29.7)**	**27 (22.7)**	**13 (11.0)**	**.003**
Hypercholesterolemia, n (%)	327 (69.0)	84 (70.6)	87 (73.7)	80 (67.2)	76 (64.4)	.48
Hypertension, n (%)	**285 (60.1)**	**67 (56.3)**	**77 (65.3)**	**82 (68.9)**	**59 (50.0)**	**.016**

	Total sample (n = 474)	Quartile 1 (n = 119)	Quartile 2 (n = 118)	Quartile 3 (n = 119)	Quartile 4 (n = 118)	P-value
Table 1 (Continued)						
BMI, mean (SD)	**26.8 (4.7)**	**27.9 (6.6)**	**26.5 (4.1)**	**27.1 (4.0)**	**25.9 (3.3)**	**.011**
COPD, n (%)	**78 (16.5)**	**29 (24.4)**	**26 (22.0)**	**14 (11.8)**	**9 (7.6)**	**<.001**
Renal dysfunction, n (%)	44 (9.3)	12 (10.1)	14 (11.9)	12 (10.1)	6 (5.1)	.35
Back pain, n (%)	**69 (14.6)**	**35 (29.4)**	**15 (12.7)**	**11 (9.2)**	**8 (6.8)**	**<.0001**
Hip or knee osteoarthritis, n (%)	98 (20.7)	33 (27.7)	26 (22.0)	19 (16.0)	20 (17.0)	.10
Vascular laboratory assessment						
PFWD, median (SD), m	**80.0 (123.9)**	**70.0 (67.1)**	**80.0 (120.0)**	**80.0 (136.9)**	**100.0 (147.6)**	**<.0001**
Resting ABI, mean (SD)*	65.9 (16.6)	63.2 (18.2)	66.7 (17.7)	68.1 (14.6)	65.8 (15.2)	.13
Prior lower-extremity revascularization						
Endovascular, n (%)	60 (12.7)	23 (19.3)	13 (11.0)	14 (11.8)	10 (8.5)	.07
Surgery, n (%)	**33 (7.0)**	**17 (14.3)**	**8 (6.8)**	**5 (4.2)**	**3 (2.5)**	**.002**
Anatomical lesion location						**.021**
Proximal, n (%)	**129 (28.5)**	**34 (31.8)**	**36 (31.9)**	**34 (29.1)**	**25 (21.7)**	
Distal, n (%)	**234 (51.8)**	**46 (43.0)**	**53 (46.9)**	**60 (51.3)**	**75 (65.2)**	
Proximal and distal, n (%)	**44 (9.7)**	**9 (8.4)**	**11 (9.7)**	**13 (11.1)**	**11 (9.6)**	
Non-significant, n (%)	**45 (10.0)**	**18 (16.8)**	**13 (11.5)**	**10 (8.6)**	**4 (3.4)**	
Medication use						
Aspirin, n (%)	368 (77.6)	90 (75.6)	93 (78.8)	93 (78.2)	92 (78.0)	.96
Anticoagulants, n (%)	**78 (16.5)**	**25 (21.0)**	**27 (22.9)**	**14 (11.8)**	**12 (10.2)**	**.013**
Statins, n (%)	391 (82.5)	98 (82.4)	102 (86.4)	101 (84.9)	90 (76.3)	.20
Beta blocker, n (%)	205 (43.2)	49 (41.2)	62 (52.5)	53 (44.5)	41 (34.7)	.050

	Total sample (n = 474)	Quartile 1 (n = 119)	Quartile 2 (n = 118)	Quartile 3 (n = 119)	Quartile 4 (n = 118)	P-value
Table 1 (Continued)						
Diuretics, n (%)	**113 (23.8)**	**35 (29.4)**	**32 (27.1)**	**30 (25.2)**	**16 (13.6)**	**.025**
ACE inhibitor, n (%)	157 (33.1)	45 (37.8)	44 (37.3)	39 (32.8)	29 (24.6)	.11
Calcium antagonist, n (%)	**102 (21.5)**	**25 (21.0)**	**26 (22.0)**	**35 (29.4)**	**16 (13.6)**	**.024**
Nitroglycerin, n (%)	**42 (8.9)**	**16 (13.5)**	**12 (10.2)**	**10 (8.4)**	**4 (3.4)**	**.050**
Digoxin, n (%)	9 (1.9)	3 (2.5)	3 (2.5)	3 (2.5)	0 (0.0)	.34
Antiarrhythmics, n (%)	12 (2.5)	5 (4.2)	3 (2.5)	3 (2.5)	1 (0.9)	.44
Antidepressants, n (%)	**26 (5.5)**	**15 (12.6)**	**4 (3.4)**	**4 (3.4)**	**3 (2.5)**	**.001**
Anxiolytics, n (%)	19 (4.0)	8 (6.7)	7 (5.9)	2 (1.7)	2 (1.7)	.10
Hypnotics, n (%)	**22 (4.6)**	**10 (8.4)**	**7 (5.9)**	**4 (3.4)**	**1 (0.9)**	**.035**
Psychological factors						
Depression, n (%)	**131 (27.9)**	**62 (52.1)**	**36 (30.8)**	**25 (21.6)**	**8 (6.8)**	**<.0001**
Anxiety, n (%)	**109 (23.2)**	**45 (37.8)**	**29 (24.8)**	**30 (25.9)**	**5 (4.2)**	**<.0001**
Type D personality, n (%)	**104 (22.3)**	**39 (33.3)**	**33 (28.2)**	**19 (16.4)**	**13 (11.0)**	**<.0001**

Quartile 1 = PCS12 ≤31.5, Quartile 2 = PCS12 31.6-38.5, Quartile 3 = PCS12 38.6-46.8, Quartile 4 = PCS12 ≥46.9. Abbreviations: ABI = ankle-brachial index; ACE inhibitor = angiotensin-converting-enzyme inhibitor; BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; PCI = percutaneous coronary intervention; PFWD = pain-free walking distance; SD = standard deviation; TIA = transient ischemic attack. *lowest ABI measured.

Figure 2 – Scatter plot of 1-year health status change scores by baseline health status scores. All change scores of individual patients included in the analyses are presented as a function of the receipt of invasive (black) vs. non-invasive (white) treatment.



Abbreviation: PCS = physical component score.

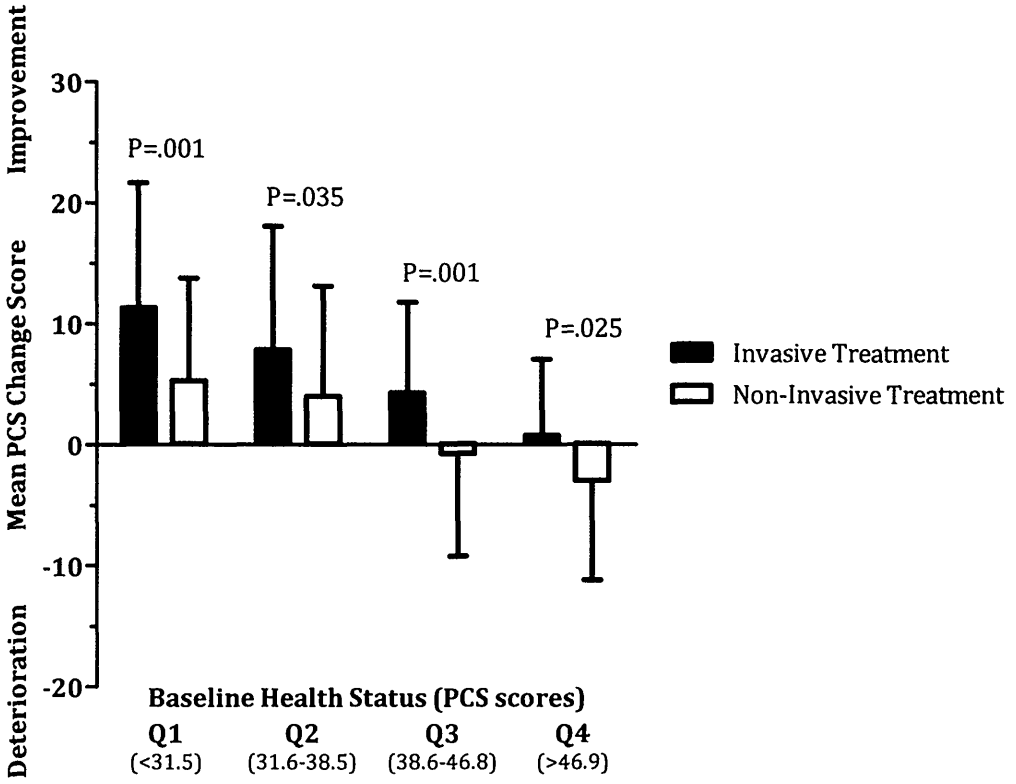
These observations were replicated when comparing the mean 1-year health status change scores by the receipt of invasive vs. non-invasive treatment (Figure 3). Patients in the lowest quartile undergoing invasive treatment had the greatest health status improvement (mean health status change scores range from 5.3 to 11.3) whereas those in the highest quartile only improved minimally or deteriorated (mean health status change scores range from -3.0 to 0.8).

Patients with pre-procedural health status scores in the lowest quartile who were treated invasively obtained larger health status benefits as compared with patients who did not receive invasive treatment (mean±SD PCS score for invasive treatment=11.3±10.3 vs. mean±SD PCS score for non-invasive treatment=5.3±8.5, P=.001; Cohen's D=0.5; NNT=3 to obtain 0.5 SD improvement; NNT=3 to obtain 1 SD improvement). Patients with pre-procedural health status scores in the highest quartile had the least benefit, when treated invasively (mean±SD PCS score for invasive treatment=0.8±6.3 vs. mean±SD for non-invasive treatment=-3.0±8.2, P=.025; Cohen's D=0.4, NNT=5 to obtain 0.5 SD improvement; NNT=90 to obtain 1 SD improvement). Similarly, for the intermediate quartiles, higher proportions of patients obtaining clinical benefit from invasive treatment were observed among those who had lower pre-procedural health status scores (Figure 3, Table 2).

Determinants of 1-year change in self-reported physical health status

Invasive treatment within 1-year following PAD diagnosis was independently associated with greater improvements in 1-year physical health status (unadjusted B=5.49; 95%CI 3.74;7.25, P<.0001; fully-adjusted B=2.39. 95%CI 0.04;4.73, P=.046) (Table 3 for stepwise results). Other correlates of greater 1-year health status improvements were lower pre-procedural health status scores, a greater 1-year change in patients' ABI, and the absence of diabetes mellitus and depression. The variables in the model explained between 0-22% of the total variance, with pre-procedural health status explaining the most (R^2=0.22). The interaction between 1-year treatment strategy and pre-procedural PCS scores was not included in the model, because it failed to reach significance (P=.44). Full model results are presented in Appendix 1. Results were essentially replicated when repeating analyses based on complete cases (results available from the authors).

Figure 3 - Mean (SD) changes in 1-year health status scores for patients that received invasive vs. non-invasive treatment, stratified by quartile categories of baseline health status scores. Bars represent mean PCS change scores and its standard deviation for patients undergoing invasive vs. non-invasive treatment. Categories represent baseline quartiles of physical health status scores for invasive vs. non-invasive treatment. Q1=lowest quartile, Q4=highest quartile.



Abbreviations: PCS=physical component score, SD=standard deviation, Q=Quartile.

Table 2 – The number needed to treat for 1-year clinically relevant health status improvement (≥5 or ≥10 points) for quartiles of patients' baseline health status scores, stratified by invasive vs. non-invasive treatment.

	Improvement			
	≥5 points	**NNT**	**≥10 points**	**NNT**
Quartile 1		3		3
Invasive treatment, n / total n (%)	34 / 48 (71)		27 / 48 (56)	
Non-invasive treatment, n / total n (%)	28 / 71 (39)		17 / 71 (24)	
Quartile 2		11		9
Invasive treatment, n / total n (%)	29 / 52 (56)		21 / 52 (40)	
Non-invasive treatment, n / total n (%)	31 / 66 (47)		20 / 66 (30)	
Quartile 3		4		7
Invasive treatment, n / total n (%)	28 / 55 (51)		15 / 55 (27)	
Non-invasive treatment, n / total n (%)	17 / 64 (27)		9 / 64 (14)	
Quartile 4		5		90
Invasive treatment, n / total n (%)	8 / 28 (29)		0 / 28 (0)	
Non-invasive treatment, n / total n (%)	10 / 90 (11)		1 / 90 (1)	

Abbreviation: NNT = number needed to treat to obtain ≥5 points (=0.5 standard deviation) or ≥10 points (=1.0 standard deviation) change in 1-year PCS score.

Table 3 – The unadjusted and adjusted linear regression model results for 1-year change in physical health status. B and 95% confidence intervals (CI) are presented.

	B	95% CI	P value
Unadjusted			
Invasive Treatment	**5.49**	**3.74;7.25**	**<.0001**
Adjusted 1*			
Invasive Treatment	**4.48**	**2.25;6.72**	**<.0001**
Baseline PCS12 Score	**-0.38**	**-0.48;-0.27**	**<.0001**
Adjusted 2†			
Invasive Treatment	**4.39**	**2.17;6.62**	**<.0001**
Baseline PCS12 Score	**-0.38**	**-0.49;-0.27**	**<.0001**
Adjusted 3‡			
Invasive Treatment	**2.44**	**0.05;4.83**	**.046**
Baseline PCS12 Score	**-0.40**	**-0.51;-0.29**	**<.0001**
Adjusted 4§			
Invasive Treatment	2.21	-0.17;4.58	.07
Baseline PCS12 Score	**-0.48**	**-0.59;-0.36**	**<.0001**
Adjusted 5‖			
Invasive Treatment	**2.39**	**0.04;4.73**	**.046**
Baseline PCS12 Score	**-0.52**	**-0.64;-0.41**	**<.0001**

The following variables are sequentially included in the adjusted models: *adjusted model 1 = 1-year treatment strategy (invasive vs. non-invasive) and baseline PCS scores; †adjusted model 2 = model 1 and demographics (age, sex), hospital site, marital status (partner vs. no partner), educational background (≥high school education vs. <high school education); ‡adjusted model 3 = model 2 and anatomical lesion location (proximal lesions only, distal lesions only, both proximal and distal lesion, or non-significant lesions), 1-year change in resting ABI (1-year ABI at rest minus baseline ABI at rest); §adjusted model 4 = model 3 and cardiac history, cerebrovascular history, current smoking, diabetes mellitus, BMI, renal failure, COPD, back pain and hip or knee osteoarthritis; ‖adjusted model 5 = model 4 and depression. Full model results are presented in Appendix 1.

DISCUSSION

This study was the first to prospectively describe health status changes following 1-year management of patients' PAD symptoms at specialty clinics in a cohort of newly diagnosed patients who had access to non-invasive as well as invasive treatment options. We described these changes as a function of patients' pre-procedural health status, which never has been done before in this population. While patients with lower pre-procedural health status scores tend to have more comorbidities, health status benefits at 1-year follow-up for those who were referred to invasive treatment were among the highest, as compared with patients who had higher health status scores. Putting these numbers into perspective, we calculated that only 3 patients needed to be treated invasively in the group with low pre-procedural health status scores in order for 1 patient to obtain a significant health status benefit, as compared with 5 patients to be treated among those with high pre-procedural health status scores. This number even increased up to 90 patients if we varied the threshold for a minimal clinical important difference from 0.5 SD to 1 SD, a threshold that approximates the magnitude of benefit observed in the latest CLEVER results for those treated invasively vs. non-invasively.[2] Important to note was that invasive treatment referral was substantial: close to half of the patients with pre-procedural health status scores in the lower quartiles underwent invasive treatment, and about 1 in 5 in patients who had the highest physical health status scores upon PAD diagnosis. Undergoing invasive treatment and pre-procedural health status scores were important independent correlates of 1-year health status changes, even while adjusting for demographics, lesion location, clinical risk factors, and depression.

Although it has been evaluated before in smaller observational studies that invasive treatment in PAD is associated with improvements in health status changes,[4, 28, 29] none of these were able to describe health status changes as a function of patients' pre-procedural health status scores. Having a cohort at our disposal that was newly evaluated for their PAD symptoms, and that had access to non-invasive or invasive options is unique, as the few studies available that quantify health status after revascularization have been done in procedural cohorts, where patients were already triaged to undergo invasive treatment,[30-33] and no information on pre-procedural

considerations with regards to patients' health status had been analyzed.[32] As prior studies that quantified benefits of invasive treatment in PAD may have traditionally focused on hemodynamic success rates,[7-9] there is clearly a need to do the same for outcomes that are more meaningful to the individual patient. This is further underscored by current PAD guidelines stating that the main treatment goals for PAD are to relieve PAD symptoms and to improve patients' health status.[1, 3, 34] Our study specifically focuses on this goal and provides useful information on patients' expected health status gains, information that will help both patients and clinicians make informed decisions about which PAD treatment strategies would fit them most.

Prior studies found that patients undergoing invasive treatment reported significant improvements in their post-procedural self-reported health status as compared with their health status scores prior to treatment.[4, 28, 30-33] These studies mainly included observational single-center cohorts that prospectively evaluated patients' health status.[4, 28, 30-33] However, these studies did not identify easy access to pre-procedural patient information that robustly predicts health status benefits after treatment referral. Our study did use such easy to measure information – pre-procedural health status – and found that this factor explained over one fifth of the variation in our model quantifying 1-year health status changes. Providing this information to patients and clinicians would be tremendously helpful, as they now can only rely on very little pre-procedural information – such as lesion characteristics that may be more amenable to invasive treatment – [1, 3] that can help decide which treatment would be of interest to the individual patient. Patients and clinicians should be aware of the fact that a wide variation in pre-procedural health status scores exists, despite having a relatively comparable clinical and disease-severity profile, and that – according to our results – patients already scoring in the top for their health status, are unlikely going to benefit from an invasive procedure as far as their health status concerns. These observations also raise the question whether given these limited gains to expect in patients already having a high pre-procedural health status; patients should be unnecessarily exposed to the risks of undergoing an invasive procedure?

After all, all patients undergoing lower-extremity endovascular interventions are exposed to various procedural-related risks and complications (range 4-8%)[35] such as access-related risks (e.g., bleeding, hematomas) and needing a repeat procedure due to the occlusion of the vessel.[36, 37] In contrast, serious events for non-invasive options including supervised exercise training have rarely been documented, but benefits can equally be present including improvements in patients' walking abilities,[1, 38, 39] muscle strength/endurance, and cardiac function.[1, 40] There should be a free flow of information on risks and benefits to patients when clinicians are discussing treatment options with their patients and patients' preferences should be additionally taken into account when a treatment decision is to be made. These efforts will eventually help to improve the decisional quality in PAD and may hopefully set the stage to start thinking about ways to design appropriateness use criteria for invasive treatment options in PAD. In these future criteria, decisional quality should have a prominent role.

Future research efforts will be needed to better document the individual components of decisional quality in PAD – including a better evidence-base on risks and benefits (including health status benefits) to be expected for different types of treatments and information on patient preferences. Parallel with these efforts, an agreed-upon classification system for diagnostic information is a prerequisite to help standardizing the clinical decision process in PAD. These efforts have already been done and are ongoing for patients with coronary artery disease,[41] but are still greatly lacking in PAD. All these efforts will eventually help reduce unwanted treatment variations in PAD.

The following limitations should be noted when interpreting the results: The generic SF-12 was used to assess patients' self-reported health status and not a PAD-specific health status assessment tool. Captured changes may be even more pronounced when using a disease-specific instrument such as the Peripheral Artery Questionnaire,[42, 43] and if anything, the use of a generic instrument may have led to an underestimation of the documented effects. We also did not have information on patient preferences at our disposal, which would have given us better insight into why certain decisions would have been made.

Next, we recruited patients from 2 vascular specialty clinics in the Netherlands, and as such, our results may have limited generalizability to other contexts. Furthermore, the time interval between eventual intervention and the 1-year evaluation was not equal in the studied patients. Differences in this time interval might have influenced our results. Finally, despite our methodological efforts to help overcome the differences across patients who underwent invasive vs. non-invasive treatment, we relied on observational data, and should acknowledge that the risk of residual confounding remains.

CONCLUSIONS

This study was able to predict which patients will benefit most from invasive treatment in PAD, based on pre-procedural information that is both meaningful to patients as well as clinicians. Pre-procedural health status was an important indicator of treatment benefit as it explained most of the variance in 1-year changes in health status following PAD management in vascular specialty clinics. Our findings will be an important impetus to develop further research that aims to document expected outcomes – including health status outcomes – as a function of a myriad of treatments available to patients with PAD as well as individual patient characteristics, such that this information can be used to have productive discussions between patients and clinicians about which treatment would be most appropriate and preferable to the individual patient.

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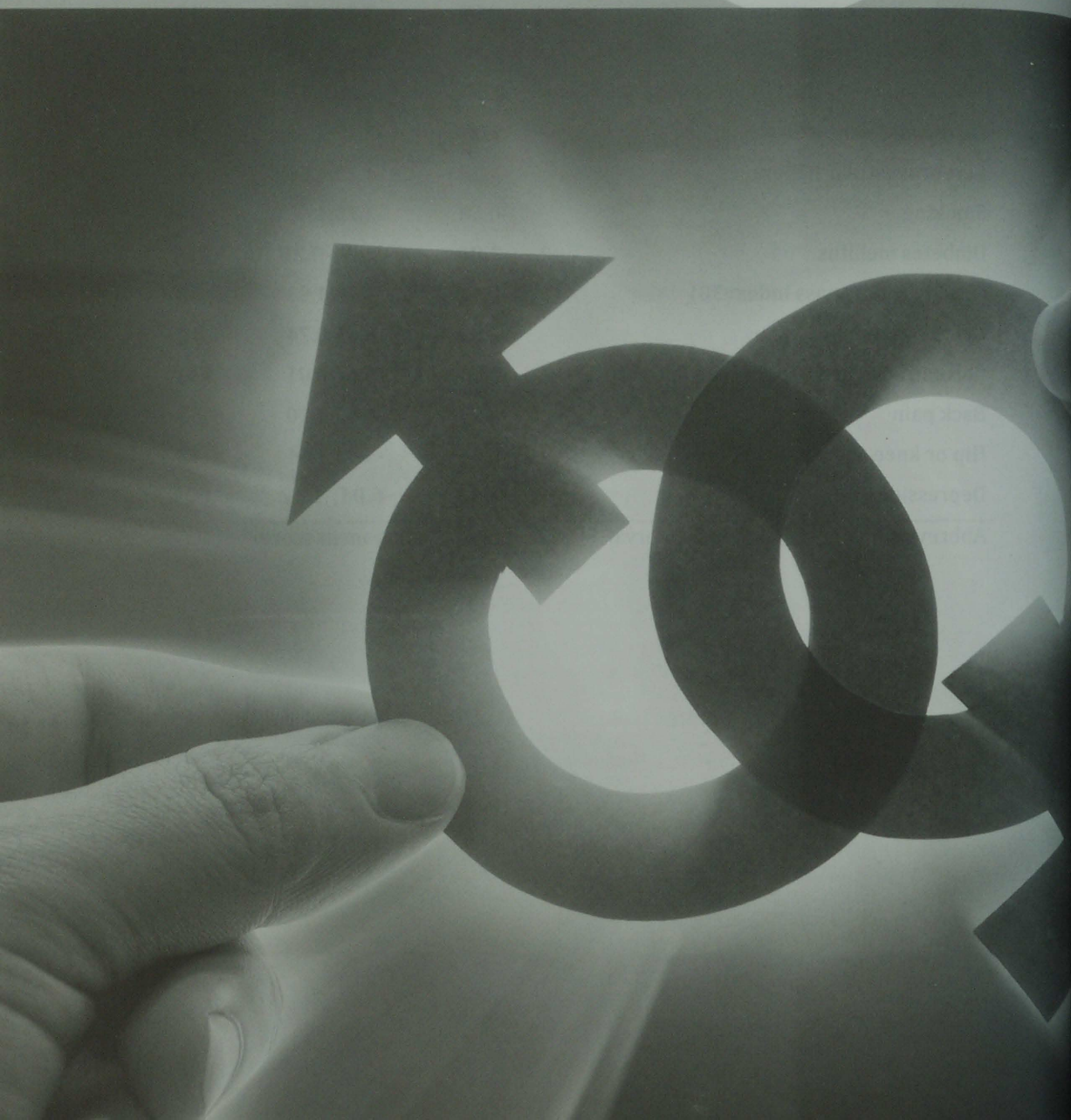
APPENDIX 1 – Full model results for 1-year changes in physical health status.

	B	95%CI	P-value
Invasive Treatment	**2.39**	**0.04;4.73**	**.046**
Baseline PCS12	**-0.52**	**-0.64;-0.41**	**<.0001**
Age	-0.11	-0.25;0.03	.11
Male gender	-0.20	-2.50;2.11	.87
Hospital Site	2.84	-5.84;11.52	.52
No Partner	-0.89	-3.60;1.83	.52
<High school education	-0.85	-3.24;1.55	.49
Anatomical lesion location	0.20	-1.14;1.54	.77
1-Year ankle-brachial index change	**0.10**	**0.04;0.16**	**.001**
Cardiovascular history	0.08	-2.17;2.33	.94
Cerebrovascular history	-1.18	-4.23;1.86	.45
Smoking	-0.58	-2.75;1.60	.60
Diabetes mellitus	**-2.86**	**-5.47;-0.25**	**.032**
Obesity (body mass index>30)	-0.91	-3.76;1.93	.53
Renal dysfunction	-2.83	-6.41;0.74	.12
Chronic obstructive pulmonary disease	-2.83	-5.67;0.01	.050
Back pain	-0.98	-4.05;2.10	.53
Hip or knee osteoarthritis	-0.94	-3.52;1.64	.47
Depression	**-3.58**	**-6.04;-1.12**	**.004**

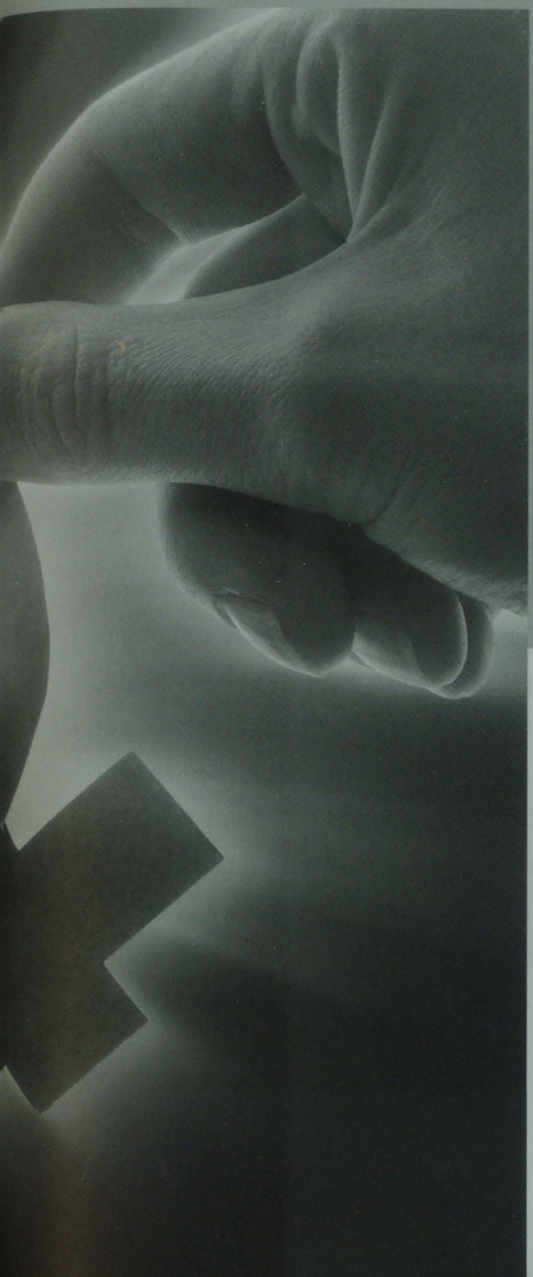
Abbreviations: CI = confidence interval, PCS12 = physical component score.

Chapter 6



Gender differences

in health status and adverse outcomes amongst patients with peripheral arterial disease



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R.P. Dreyer, M. van Zitteren, J.F. Beltrame, R. Fitridge, J. Denollet, P.W. Vriens, J.A. Spertus, K.G. Smolderen. Gender differences in health status and adverse outcomes amongst patients with peripheral arterial disease. *Submitted.*

ABSTRACT

Background: Few studies have examined gender differences in health status and cardiovascular outcomes in patients with peripheral artery disease (PAD). This study assessed (a) self-reported symptomatic health status at PAD diagnosis and 12-month follow-up, and explored (b) whether outcomes in women with PAD differ with regards to 3.2-year major adverse events.

Methods: A total of 816 patients (531 men, 285 women) with PAD were consecutively enrolled from 2 vascular clinics in the Netherlands. Clinical details/adverse events were recorded and patients completed the Short Form 12 (SF-12, Physical Component Score [PCS] and Mental Component Score [MCS]) upon PAD diagnosis and 12-months later. Median regression models were used to examine the relationship between gender and health status. Kaplan Meier curves and Cox proportional hazards models were constructed to explore the association between gender and all-cause mortality/major adverse events.

Results: Women and men had similar ages and clinical characteristics, however women had a poorer socioeconomic background and suffered from more depressive symptoms at initial diagnosis. Women also had poorer physical (median PCS: 37±10 vs. 40±10, P=.004) and mental (median MCS: 47±12 vs. 49±11, P=.005) health status at the time of presentation, as compared with their male counterparts. At 12-months, women still reported a poorer overall PCS score (median PCS: 41±12 vs. 46±11, P=.006) and MCS score (median MCS: 42±14 vs. 49±12, P=.002). In multivariable analysis, female gender was an independent determinant of poorer baseline PCS and MCS scores and at 12-month follow-up. There was no significant difference by gender on either mortality (unadjusted HR=0.93, 95%CI 0.60;1.44, P=.74) or major adverse events (unadjusted HR=0.90, 95%CI 0.63;1.29, P=.57).

Conclusions: In a real-world setting, women's physical and mental health status is compromised both at initial PAD diagnosis and 12-month follow-up, despite experiencing a similar magnitude of change in their health scores throughout the first 12-months after diagnosis. Female PAD patients do seem to have similar prognostic expectations as compared with men.

INTRODUCTION

Peripheral arterial disease (PAD), along with coronary and cerebrovascular disease, constitutes the leading cause of morbidity and mortality worldwide.[1, 2] While PAD affects up to 20% of the population aged 65 years or older, the disease has received less attention as compared with other atherothrombotic disorders in terms of its recognition and treatment of cardiovascular risk factors.[3-6] Furthermore, PAD may be even more disabling than other vascular diseases,[7, 8] not only because of its impact on patients' health status (their symptoms, function and quality of life), but also due to it's high event rate.[7, 9, 10]

Gender-based disparities in health status and outcomes of PAD patients have also not been as extensively investigated, as compared with coronary artery disease (CAD), where such differences have been documented in great detail. For example, women with CAD are confronted with poorer health status outcomes,[11] have increased in-hospital and long-term mortality,[12-14] and increased mortality following cardiac revascularization procedures.[15, 16] In contrast, major knowledge gaps exist in terms of gender-specific differences in the health status of PAD patients and their cardiovascular mortality rates. Preliminary data available suggest that women suffer more from depression,[17] experience more atypical lower-extremity symptoms, and have a poorer overall health status as compared with men.[18,19,20-26] In addition, women with PAD have an increased risk for morbidity and mortality,[27] however; no study has explicitly focused on differences between men and women.

With these factors in mind, the current study was designed to assess potential explanatory factors for gender-based differences in outcomes (health status and long-term adverse prognosis), including exploring the explanatory role of depressive symptoms for these outcomes.[17] Most prior work examining PAD and gender-based differences were cross-sectional studies or were not explicitly addressing gender differences in their primary objectives and analyses.

More prospective research is needed to illuminate potential gender differences in PAD. Consistent with these observations, the recent scientific statement from the American Heart Association (AHA) issued a 'call to action' for more focused care and research that is sensitive to the specific concerns of women with PAD.[28]

Since potential gender disparities in self-reported health status and adverse outcomes following PAD diagnosis have not been prospectively quantified, the current study aimed to prospectively evaluate whether outcomes in women with PAD differ with regards to their self-reported symptomatic health status outcomes and the occurrence of long-term major adverse events. The underlying hypothesis was that women would have poorer outcomes, including a poorer self-reported health status, increased mortality and an increased adverse event burden as compared with men.

METHODS

Participants

Participants with newly diagnosed symptomatic PAD or with an exacerbation of existing PAD symptoms were consecutively enrolled from 2 vascular outpatient clinics of the St. Elisabeth Hospital (March 2006-November 2011) and TweeSteden Hospital (March 2006-October 2008) in Tilburg, the Netherlands. Study entry criteria for PAD patients included having symptomatic PAD and an abnormal resting ankle-brachial index (ABI) (≤0.90)[29] or an abnormal post-exercise ABI (ABI decrease of 15% following exercise). Exclusion criteria included patients with critical leg ischemia, significant cognitive impairment, severe psychiatric co-morbidities (e.g., psychosis), life threatening or debilitating conditions that prevented participation (e.g., undergoing active cancer treatment), and insufficient knowledge of Dutch language and/or illiteracy. Patients with a non-compressible ABI (≥1.30) were also excluded.

The protocol was designed according to the Helsinki declaration and approved by the local ethics committees of the participating hospitals. All participants provided written informed consent. Patients were invited to participate in the study by their treating vascular surgeon during their visit at one of the outpatient clinics, following a vascular diagnostic work-up that confirmed the presence of PAD. All patients within the study completed a set of specific questionnaires collected by mail following recruitment at baseline as well as at 12-month follow-up. Demographic, risk factor, medication, and therapeutic information were obtained by abstracting patients' medical records.

MEASURES

Health status

The Dutch version of the Short Form 12 (SF-12) was administered to assess health status,[30, 31] both at baseline and 12-months later. This generic tool measures overall physical and mental health status and consists of 12 items with standard Likert scales.

Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores[32] are generated through a standardized scoring algorithm and were based on weights derived from Dutch population norms (score ranges between 0-100, mean score=50, SD=10), with higher scores indicating better functioning.[33] The SF-12 has been demonstrated to be a valid and reliable instrument[30] and has been successfully used before in PAD populations.[7, 34]

Depressive symptoms

The 14-item self-report Hospital Anxiety and Depression Scale (HADS) was used to measure self-report depressive symptoms in the PAD population. Criterion scores of ≥8 for the depression subscale denoted clinically relevant symptoms of depression.[35]

All-cause mortality and adverse events

The major adverse events studied included (1) all-cause mortality and (2) acute myocardial infarction (AMI) that was diagnosed by a cardiologist and required hospitalization, (3) stroke that was diagnosed by a neurologist and required hospitalization, and (4) any PAD related lower-extremity amputation (e.g., amputation of toes or part of the foot, below or above knee amputation, and through knee amputation due to PAD, excluding traumatic amputations). Mortality was used both as a separate outcome of interest and also as a combined endpoint with the other major adverse events. Information on adverse events were documented from patients' medical records by a surgical fellow under supervision of two vascular surgeons, since diagnosis of PAD until January 1st 2012. For mortality, in-hospital mortality as well as mortality events outside the hospital were documented as patients' medical records are linked to the regional social security death index of the Tilburg community; deaths occurring outside the Tilburg community were passed on by patients' general practitioners.

Ankle-brachial index

The vascular laboratory assessment procedures have been described previously.[36] In brief, a handheld Doppler ultrasonic instrument was used to obtain systolic blood pressure readings in the right and left brachial arteries, right and left dorsalis pedis arteries, and right and left posterior tibial arteries. The ABI at rest and after walking on a treadmill (distance limited 1000 meters) was obtained with the lower resting ABI used in all analyses. In all patients, the pain-free walking distance, maximum treadmill walking distance and the ABI index were measured as indices of severity of PAD, whereby the ABI is defined as the ratio of the ankle systolic blood pressure to the brachial artery systolic blood pressure and has a normal resting value of approximately 1.0.[37] A value of <0.90 has been shown to be highly sensitive to detect PAD.[38]

Sociodemographics and clinical variables

Age and gender were abstracted from medical records and information on sociodemographics was self-reported by the patients. These included marital status (not having a partner vs. having a partner), high school education or more (less than high school education vs. high school education or more) and work status (active vs. non-active working status). Clinical variables for patients were obtained from medical records at baseline and included: cardiovascular risk factors (current smoking, hypercholesterolemia, hypertension, diabetes mellitus, chronic heart failure), cardiovascular history (previous AMI, angina, coronary artery bypass grafting, percutaneous coronary intervention, stroke, and transient ischemic attack), co-morbidities (renal dysfunction, chronic obstructive pulmonary disease [COPD], body mass index [BMI, kg/m^2], prior documented back pain, prior documented knee/hip osteoarthritis, and depression) and PAD clinical factors (resting and post-exercise ABI, pain free walking distance, and maximum walking distance). Medications that patients were taking upon enrollment were abstracted from their medical charts and included aspirin, statins, anticoagulants, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, diuretics, nitrates and antiarrthymics (including digoxin), antidepressants, anxioltyics, and hypnotics.

Statistical Analysis

Baseline characteristics were examined for the total sample and compared between genders. In addition, baseline and 12-month follow-up health status scores were examined for the total population and stratified by gender. The Student's t-tests and Wilcoxon tests were used for continuous variables and Chi-square tests or Fisher's Exact tests were used for categorical variables, as appropriate.

For the health status analyses, 6 sets of median regression models examined the relationship between gender, and (1) baseline health status scores (baseline PCS12 and MCS12), (2) 12-month health status scores (12-month PCS12 and MCS12), and (3) health status change scores (12-month PCS12/MCS12 scores minus baseline PCS12/MCS12 scores). Median regression was performed due to non-linear distribution of the health status scores. The following variables were sequentially entered into the models: demographics (gender, age), sociodemographics (marital status, educational level), cardiovascular risk factors and cardiovascular history (diabetes, current smoking, prior stroke, prior AMI, heart failure, and renal dysfunction). In two exploratory steps, depression was included into the model first, and obesity (BMI $\geq$30 vs. <30), COPD, back pain, and knee/hip osteoarthritis thereafter. An interaction term between gender and age for SF-12 scores was evaluated, but not included in the final models, as it was not significant in any of the analyses.

Missing SF-12 items were assumed to be missing at random and handled by multiple imputation (mean of 5 iterations) if $\geq$75% of all items were complete at baseline and 12-months. The pooled estimates and 95% confidence intervals (CI) for the 5 imputed datasets were used. A comparison of baseline characteristics was conducted for those who were included in the SF-12 analyses (0-25% missing) vs. those who were eligible for inclusion but who were not in the SF-12 analyses (>25% missing). Baseline characteristics were similar between these groups, however patients not in the analyses were more likely to be women (Cramér's V=0.079), smokers (Cramér's V=0.083) or to have a higher maximum walking distance (Cohen's D=0.15) as compared with those who were included in the SF-12 analyses (all effect sizes were small).

Two sets of Cox proportional hazards models were constructed to examine the relationship between gender and (1) all-cause mortality and (2) major adverse events outcomes (i.e., all-cause mortality, AMI, stroke, and lower-extremity amputation). As our study was mainly powered to evaluate unadjusted associations between gender and adverse prognosis, the following 2 multivariable Cox proportional hazard analyses (one for all-cause mortality and one for major adverse events) were only conducted for exploratory and hypothesis-generating reasons. Both models were sequentially built including the following variables: demographics (gender, age), cardiovascular risk factors and cardiovascular history (diabetes mellitus, current smoking, prior stroke, prior AMI, heart failure, and renal dysfunction). Socioeconomic factors (marital status, educational level) and depression were only added as an exploratory last step. We assessed an interaction term between gender and age for all-cause mortality and major adverse cardiac event outcomes, but in both analyses the interaction terms were not significant (P=.72, P=.49, respectively) and thus were excluded from the final multivariable model.

All tests were two-tailed and a P-value <.05 was considered statistically significant. All analyses were performed using SPSS 17.0 for Windows (PASW Inc., Chicago Ill) and SAS Software version 9.2. (SAS Institute Inc, Cary, North Carolina).

RESULTS

Patient characteristics

Baseline characteristics of the total sample (n=816) were stratified by gender and listed in Table 1. The mean age of the total cohort was 65 years and 285 (35%) were women. Both men and women were similar in terms of age, cardiovascular risk factors, medical history and ABI values (resting and post-exercise), however women were less likely to be partnered, have high school education or more, or suffer from renal dysfunction as compared with men. In addition, women had both a significant shorter pain-free walking distance and maximal walking distance. Women also had higher rates of depressive symptoms and were more likely to be on antidepressants, anxiolytics, and hypnotics as compared with men (Table 1).

Health status analyses

In the total sample, median physical health status (PCS) improved from 39±10 at baseline to 43±11 at 12-month follow-up (median difference 2.6±10, [mean difference] 3.5±10] P<.0001). Conversely, median mental health scores (MCS) did not improve over 12-months (48±11 at baseline and 47±13 at 12-months, median difference -0.6±10, [mean difference -1.1±10] P=.12). Women, as compared with men, had poorer median physical (PCS: 37±10 vs. 40±10, P=.004) and mental (MCS: 47±12 vs. 49±11, P=.005) baseline health status scores upon being diagnosed with PAD (Figure 1). At 12-month follow-up; women still reported a poorer overall median PCS score (41±12 vs. 46±11, P=.006) and MCS score (42±14 vs. 49±12, P=.002). Women and men had similar improvement in their physical function over 12-months (median change score: 3.2±11 vs. 2.4±10) and neither group experienced a significant improvement in their mental (median change score: -1.2±12 vs. -0.6±8.8) health status.

Table 1 – Baseline demographics for the total sample and stratified by gender.

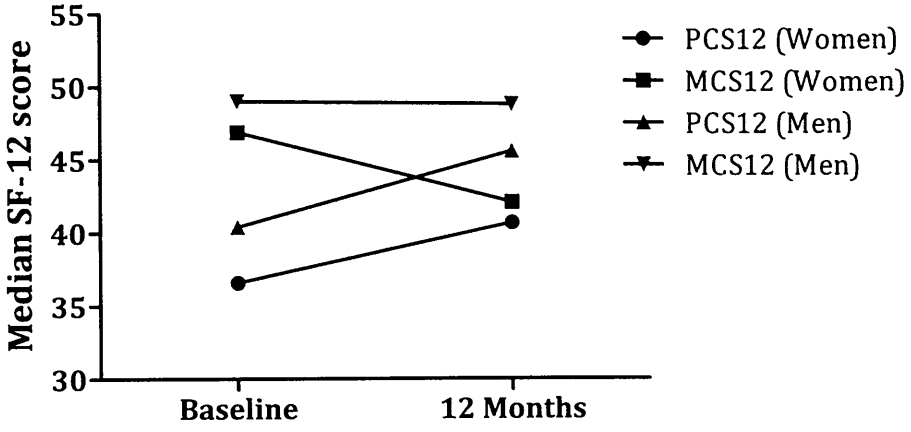
	Total sample (n=816)	Men (n=531)	Women (n=285)	P-value
Socio-demographics				
Age (mean years, SD, range)	65.3 (9.8, 37-92)	65.3 (9.6)	65.2 (10.2)	.91
No partner (n, %)	**175 (25.1)**	**75 (16.8)**	**100 (39.7)**	**<.0001**
<High school education (n, %)	**177 (25.6)**	**96 (21.5)**	**81 (32.9)**	**.001**
Non-active work status (n, %)	501 (74.4)	328 (73.9)	173 (75.5)	.64
Cardiovascular risk factors				
Current smoker (n, %)	406 (49.8)	259 (48.8)	147 (51.6)	.45
Hypercholesterolemia (n, %)	548 (67.2)	358 (67.4)	190 (66.7)	.83
Hypertension (n, %)	488 (59.8)	306 (57.6)	182 (63.9)	.08
Diabetes mellitus (n, %)	196 (24.0)	128 (24.1)	68 (23.9)	.94
Chronic heart failure (n, %)	41 (5.0)	27 (5.1)	14 (4.9)	.91
Cardiovascular history				
Myocardial infarction (n, %)	151 (18.5)	103 (19.4)	48 (16.8)	.37
Angina (n, %)	124 (15.2)	86 (16.2)	38 (13.3)	.28
Coronary artery bypass graft (n, %)	90 (11.0)	66 (12.4)	24 (8.4)	.08
Percutaneous coronary intervention (n, %)	74 (9.1)	50 (9.4)	24 (8.4)	.64
Stroke (n, %)	66 (8.1)	49 (9.2)	17 (6.0)	.10
Transient ischemic attack (n, %)	76 (9.3)	53 (10.0)	23 (8.1)	.37

	Total sample (n=816)	Men (n=531)	Women (n=285)	P-value
Table 1 (continued)				
Co-morbidities				
Renal dysfunction (n, %)	**73 (8.9)**	**56 (10.5)**	**17 (6.0)**	**.029**
COPD (n, %)	142 (17.4)	91 (17.1)	51 (17.9)	.79
Body mass index (mean, SD)	26.8 (5.0)	26.8 (4.4)	26.7 (6.0)	.82
Back pain (n, %)	126 (15.4)	76 (14.3)	50 (17.5)	.22
Knee/hip osteoarthritis (n, %)	169 (20.7)	116 (21.8)	53 (18.6)	.28
Depressive symptoms (n, %)	**186 (27.0)**	**103 (23.4)**	**83 (33.2)**	**.005**
PAD Clinical factors				
Resting ABI (mean, SD)	65.7 (16.9)	66.1 (17.1)	65.0 (16.5)	.35
Post-exercise ABI (median, SD)	36.0 (19.5)	35.0 (19.4)	36.5 (19.8)	.17
Pain-free walking distance (meters, median, SD)	80.0 (140.5)	**80.0 (143.4)**	**70.0 (133.5)**	**<.0001**
Maximum walking distance (meters, median, SD)	260.0 (313.8)	**280.0 (316.8)**	**235.0 (306.4)**	**.005**
Medications				
Aspirin (n, %)	647 (79.3)	427 (80.4)	220 (77.2)	.28
Statin (n, %)	672 (82.4)	431 (81.2)	241 (84.6)	.23
Anticoagulants (n, %)	139 (17.0)	86 (16.2)	53 (18.6)	.38
Beta blocker (n, %)	345 (42.3)	222 (41.8)	123 (43.2)	.71
Calcium channel blocker (n, %)	186 (22.8)	128 (24.1)	58 (20.4)	.22

	Total sample (n=816)	Men (n=531)	Women (n=285)	P-value
Table 1 (continued)				
ACE inhibitor (n, %)	257 (31.5)	179 (33.7)	78 (27.4)	.06
Diuretics (n, %)	206 (25.2)	128 (24.1)	78 (27.4)	.31
Nitrate (n, %)	77 (9.4)	48 (9.0)	29 (10.2)	.60
Antiarrhythmics (n, %)	21 (2.6)	12 (2.3)	9 (3.2)	.44
Antidepressants (n, %)	**48 (5.9)**	**23 (4.3)**	**25 (8.8)**	**.010**
Anxiolytics (n, %)	**34 (4.2)**	**12 (2.3)**	**22 (7.7)**	**<.0001**
Hypnotics (n, %)	**37 (4.5)**	**18 (3.4)**	**19 (6.7)**	**.032**

Abbreviations: ABI = ankle-brachial index, ACE = angiotensin-converting enzyme, COPD = chronic obstructive pulmonary disease, PAD = peripheral arterial disease, SD = standard deviation.

Figure 1 – Median physical (PCS) and mental (MCS) SF-12 summary scores at baseline and 12-month follow-up stratified by gender.



In terms of baseline physical health status (PCS scores), there was a significant effect of female gender in the unadjusted model (female B=-2.76, 95%CI -5.06;-0.46, P=.019). When adjusting for clinical factors (female B=-2.70; 95%CI -5.23;-0.16, P=.037) (adjusted step 4), depression (adjusted step 5) (female B=-2.17, 95%CI -4.28;-0.06, P=.044) and other exploratory factors (obesity [BMI ≥30 vs. <30], COPD, back pain, knee/hip osteoarthritis, adjusted step 6) (female B=-2.13; 95%CI -4.17;-0.09, P=.041), the association between female gender and lower physical health status persisted (full model results presented in Table 2; sequential modeling results in Appendix 1). In terms of baseline mental health status (MCS scores), there was a trend towards women reporting a poorer mental health status at initial PAD diagnosis as observed in the unadjusted model (female B=-2.29, 95%CI -4.98;0.40, P=.10), which became significant after adjustment for age (female B=-2.95, 95%CI -5.53;-0.37, P=.025). After full adjustment, there was no statistically significant effect of female gender in this model (female B=-1.08, 95CI -3.45;1.29, P=.37) (Table 2 and Appendix 1).

In terms of physical health status at 12-month follow-up, women tend to report a poorer physical health status (unadjusted female B=-3.89, 95%CI -7.21;-0.58, P=.023). This effect persisted when adjusting for age (female B=-3.90; 95%CI -6.75;-1.06, P=.007) and after adding depression to the model (adjusted step 5) (female B=-3.35; 95%CI -6.34;-0.37, P=.028). There was no effect of gender within the intermediate adjusted steps for PCS scores at 12-month follow-up (fully adjusted model presented in Table 3; sequential analyses in Appendix 2). With regards to patients' mental health status at 12-month follow-up, women reported a poorer mental health status (unadjusted female B=-4.66; 95%CI -8.55;-0.77, P=.019) and also following adjustment for age (female B=-4.99, 95%CI -9.07;-0.91, P=.017) and clinical factors (female B=-4.10; 95%CI -7.84;-0.36, P=.032) (adjusted step 4 in the full adjusted model).

Lastly, women's 12-month change scores for physical and mental health status did not differ significantly from that of men's, neither in the unadjusted models for PCS (female B=0.44, 95%CI -1.66;2.54, P=.68) and MCS (female B=0.35, 95%CI -1.69;2.39, P=.74), nor in the full-adjusted models for PCS (female B=-0.18, 95%CI -2.44;2.08, P=.88) and MCS (female B=-0.78, 95%CI -2.98;1.43, P=.49) (Table 4 full model results; sequential model results in Appendix 3).

Table 2 – The full adjusted model for the association between gender and baseline health status.

Regression coefficients (B) and 95% confidence intervals are presented.

	PCS12			MCS12		
	Estimate	**95% CI**	**P-value**	**Estimate**	**95% CI**	**P-value**
Female gender	**-2.70**	**-5.23;-0.16**	**.037**	-1.08	-3.45;1.29	.37
Age	0.15	0.00-0.31	.052	**0.12**	**0.00-0.23**	**.045**
No partner	-1.47	-4.10;1.17	.28	**-3.74**	**-6.58;-0.90**	**.010**
<High school education	**-2.71**	**-5.32;-0.11**	**.042**	-2.31	-5.02;0.41	.10
Diabetes	-2.54	-5.15;0.07	.06	**-3.27**	**-6.25;-0.29**	**.031**
Smoking	1.59	-0.63;3.81	.16	-0.74	-3.16;1.69	.56
Prior stroke	**-4.35**	**-7.89;-0.80**	**.016**	-2.42	-6.99;2.15	.30
Prior MI	-2.04	-4.81;0.73	.15	1.24	-1.88;4.37	.44
Heart failure	**-6.35**	**-11.94;-0.75**	**.027**	-5.88	-13.08;1.32	.11
Renal dysfunction	**-3.92**	**-7.61;-0.23**	**.039**	-3.52	-7.47;0.42	.09

Abbreviations: CI = confidence interval, MCS = mental component score, MI = myocardial infarction, PCS = physical component score.

Table 3 – The full adjusted model for the association between gender and 12-month health status.

Regression coefficients (B) and 95% confidence intervals are presented.

	PCS12 at 12-months			MCS12 at 12-months		
	Estimate	**95% CI**	**P-value**	**Estimate**	**95% CI**	**P-value**
Female gender	-3.41	-6.88;0.07	.06	**-4.10**	**-7.84;-0.36**	**.032**
Age	-0.11	-0.28;0.05	.20	0.10	-0.07;0.26	.24
No partner	-2.60	-7.11;1.90	.27	-1.29	-6.02;3.43	.59
<High school education	-3.13	-6.70;0.43	.09	**-3.76**	**-7.35;-0.17**	**.040**
Diabetes	**-5.81**	**-10.12;-1.51**	**.008**	**-5.25**	**-9.12;-1.38**	**.008**
Smoking	1.19	-2.07;4.46	.49	0.77	-2.42;3.97	.64
Prior stroke	-3.54	-9.17;2.09	.22	-0.12	-6.85;6.61	.97
Prior MI	-1.89	-5.29;1.52	.28	0.49	-3.28;4.26	.80
Heart failure	0.57	-9.70;10.84	.76	-3.81	-15.25;7.64	.51
Renal dysfunction	**-7.88**	**-13.61;-2.16**	**.008**	**-5.06**	**-9.71;-2.14**	**.033**

Abbreviations: CI = confidence interval, MCS = mental component score, MI = myocardial infarction, PCS = physical component score.

Table 4 – The full adjusted model for the association between gender and health status change scores.

Regression coefficients (B) and 95% confidence intervals are presented.

	PCS12 change scores			MCS12 change scores		
	Estimate	**95% CI**	**P-value**	**Estimate**	**95% CI**	**P-value**
Female gender	-0.18	-2.44;2.08	.88	-0.78	-2.98;1.43	.49
Age	**-0.16**	**-0.28;-0.04**	**.011**	0.01	-0.09;0.10	.89
No partner	-0.13	-2.57;2.31	.86	1.79	-0.50;4.08	.13
<High school education	-1.09	-3.05;0.87	.28	-0.16	-2.22;1.90	.85
Diabetes	-1.33	-4.18;1.53	.36	0.26	-2.07;2.59	.82
Smoking	1.07	-1.12;3.26	.34	0.70	-0.86;2.27	.39
Prior stroke	0.84	-3.98;5.67	.73	3.26	-1.84;8.36	.21
Prior MI	0.07	-2.26;2.39	.96	-0.51	-3.12;2.10	.70
Heart failure	**6.06**	**0.39;11.73**	**.045**	0.01	-5.33;0.00	.96
Renal dysfunction	-3.67	-7.77;0.44	.08	-3.83	-8.69;1.04	.14

Abbreviations: CI = confidence interval, MCS = mental component score, MI = myocardial infarction, PCS = physical component score.

Adverse event analyses

The study cohort had a median follow-up time of 3.2 years (IQR=1.7-4.5 years). During follow-up, a total of 92 (11%) deaths were documented (30 women [11%] vs. 62 men [12%]) and 138 patients (17%) experienced a first adverse event (mortality, AMI, stroke, lower-extremity amputation; 45 women [16%] vs. 93 men [18%]). The Kaplan Meier curves for all-cause mortality revealed no significant gender differences in survival time (P=.74, Figure 2). Similarly, for the onset of a first adverse event (mortality, AMI, stroke, lower-extremity amputation) there was no difference between men and women (P=.57, Figure 3).

No difference in all-cause mortality was observed between men and women in the unadjusted (unadjusted hazard ratio [HR] for women, reported for all analyses HR=0.93, 95% confidence interval [CI] 0.60;1.44, P=.74) and the final adjusted model (HR=0.86, 95%CI 0.55;1.34, P=.50) (Table 5). Older age (HR=1.05, 95%CI 1.02;1.08, P<.001), current smoking (HR=1.57, 95%CI 1.00;2.45, P=.048), heart failure (HR=3.27, 95%CI 1.80;5.92, P<.001), and renal dysfunction (HR=1.90 95%CI 1.07;3.39, P=.030) were independently associated with mortality in the final adjusted model (full model results presented in Appendix 4).

Similar results were found for the association with adverse events whereby men and women did not differ in both the unadjusted (HR for women=0.90, 95%CI 0.63;1.29, P=.57) and final adjusted model (HR=0.85, 95%CI 0.59;1.23, P=.39). Again, older age (HR=1.06, 95%CI 1.04;1.08, P=<.001), current smoking (HR=1.59, 95%CI 1.10;2.30, P=.013), prior AMI (HR=1.72, 95%CI 1.18;2.52, P=.005), and heart failure (HR=2.04, 95%CI 1.19;3.49, P=.010) were independently associated with experiencing a first adverse event in the final adjusted model (Appendix 4). Adding marital status, educational level, and depression to the models did not significantly alter the results of the event analyses (Appendix 5).

Figure 2 - Kaplan Meier survival curve for death stratified by gender.

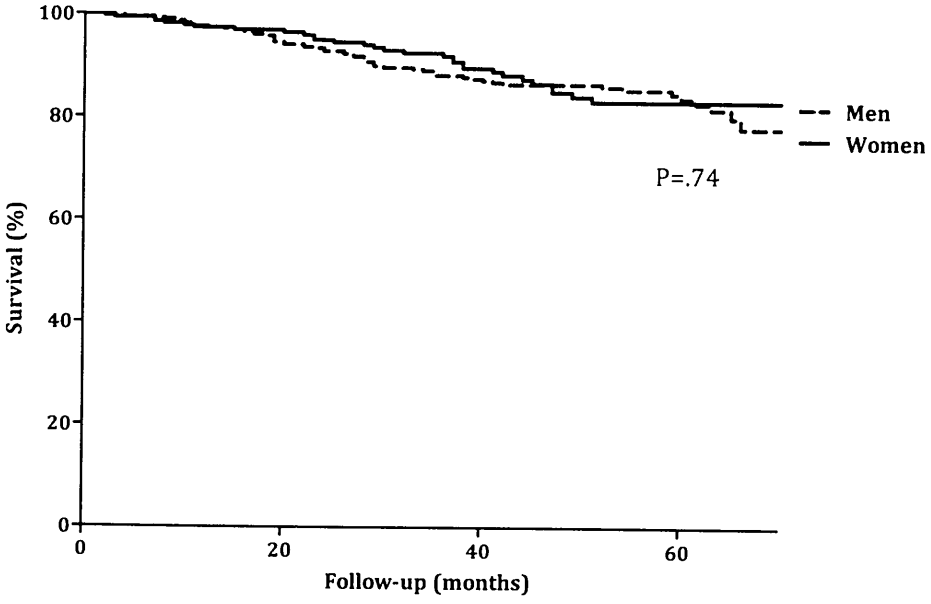


Figure 3 – Kaplan Meier survival curve for first adverse event (death, myocardial infarction, stroke, amputation) stratified by gender.

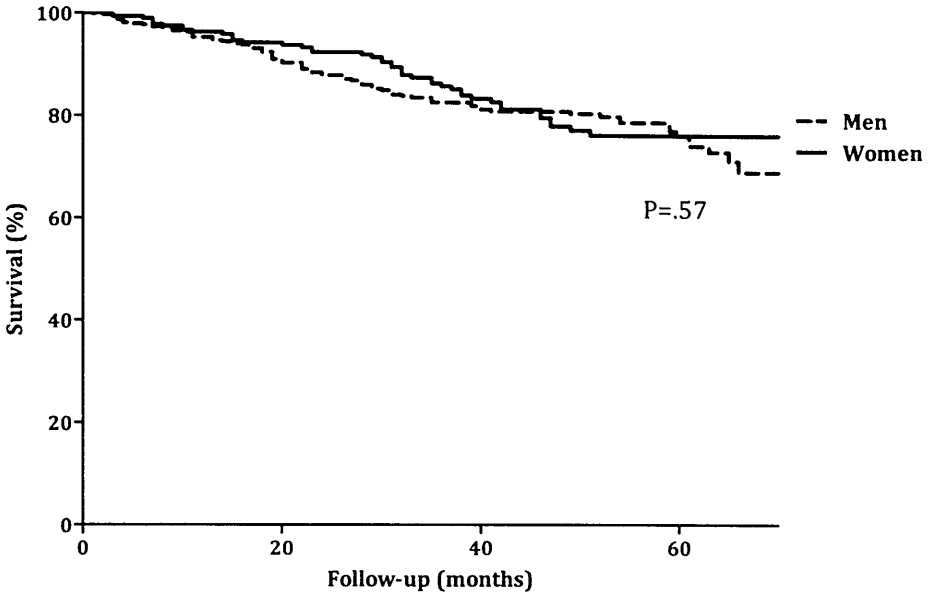


Table 5 - The unadjusted and adjusted Cox Proportional regression model between gender for mortality and all-cause adverse events (mortality, myocardial infarction, stroke, and lower-extremity amputation). Hazard ratios (HR) and 95% confidence intervals (CI) are presented.

	Mortality			Adverse events		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Unadjusted						
Female Gender	0.93	0.60;1.44	.74	0.90	0.63;1.29	.57
Adjusted 1*						
Female Gender	0.90	0.58;1.39	.63	0.87	0.61;1.24	.43
Adjusted 2†						
Female Gender	0.86	0.55;1.34	.50	0.85	0.59;1.23	.39

The following covariates are sequentially included in the adjusted models: *adjusted model 1 = gender and age; †adjusted model 2 = model 1 and clinical factors (diabetes, current smoking, prior stroke, prior acute myocardial infarction, heart failure, and renal dysfunction). See Appendix 4 for full model. Abbreviations: CI = confidence interval, HR = hazard ratio.

DISCUSSION

This study was the first to prospectively compare women's and men's outcomes following their diagnosis of PAD in a real-world setting. Since little is known about the existence of potential gender disparities in PAD, the AHA issued a scientific statement prioritizing a research agenda for this important topic.[28] Our group had data available to show that there were differences at both presentation and follow-up in terms of health status, with women reporting worse scores as compared with men. The magnitude of change in women's health status scores over 12-months was not different from the change men reported. Importantly, health status change scores for both men and women failed to reach the threshold for what is defined as a clinically relevant difference (score of ≥5-10 for a 0.5-1.0 SD change, respectively)[19, 33, 39-42] for the SF-12. These differences were largely confirmed in the multivariable regression results. With regards to our secondary aim, we were able to demonstrate that survival and cardiovascular morbidity outcomes 3 years following initial PAD diagnosis does not seem to differ between men and women.

Symptomatic health status

Women with PAD were found to have both a poorer physical and mental health status at initial diagnosis and 12-month follow-up as compared with men. More specifically, women seem to present with poor physical and mental health at baseline, with both genders equally improving in physical health over 12-months. Multivariable analyses largely confirmed that female gender was an independent predictor of a poorer physical health status at initial diagnosis as well as a determinant of a poorer mental health status at 12-months (or showed a clear trend even after extensive adjustment for confounders). These results are in line with previous studies suggesting that women with PAD have a worse health status and health-related quality of life (HRQOL) as compared with men,[20, 24-26, 43] while others have found conflicting results.[44-47]

Importantly, these absolute differences in health status scores did not exceed the threshold for a minimal clinically important difference (which is defined as a score ranging from 5 (0.5 SD) - 10 (1.0 SD) in the SF-12),[19, 33, 39-42] and as such, future studies need to further examine whether these differences are clinically meaningful to both patients and clinicians, ideally using a disease-specific instrument that is more sensitive to capturing relevant PAD-specific health status information.

Using the SF-36 in a cross-sectional study in primary care patients, Collins et al. (2008) reported that physical functioning and general health were both significantly lower for women when compared with men.[25] Similarly, Oka and colleagues utilized the same questionnaire in another smaller cross-sectional study and highlighted that despite a similar disease severity, women reported decreased physical functioning, more bodily pain and greater mood disturbance than men with PAD.[24] In their smaller prospective longitudinal study, Wann-Hansson demonstrated that female gender adversely impacted durability or quality of life following revascularization for claudication or critical limb ischemia.[43] Furthermore, Bloemenkamp and colleagues highlighted in a cross-sectional population-based study that young women (<50 years) with PAD scored lower than age matched healthy controls on all HRQOL domains on the RAND-36.[26] Finally, a mixed cohort of patients with PAD at various disease stages confirmed that women experience worse physical health, greater disability as well as poorer overall health status many years after diagnosis, however this study was limited by the lack of baseline health status data.[20] Although these preliminary studies contributed to the body of research in this field, they were limited either in terms of their small sample size, their (cross-sectional) design or did not explicitly focus on gender in their main objectives.[20] Accordingly, our study has extended the literature with results on prospectively captured health status information in a large, homogeneous PAD population before they started treatment, demonstrating that women with PAD have a compromised health status both around prognosis and 1 year after follow-up. The reason for this gender disparity is likely to be multi-factorial and requires further evaluation.

Mechanisms for poorer health status in women

The potential mechanisms contributing to the observed gender disparity in health outcomes may include differences in sociodemographics, clinical characteristics, psychosocial factors, and functional limitations. As age and cardiovascular risk profiles were similar between genders in this specific cohort, and were included as covariates in the models, we probably can rule out the potential effect this may have had on patients' health status. Furthermore, although there was no difference noted in disease severity with which these patients presented at diagnosis (as assessed by the ABI), others have proposed that differences in disease severity may explain poorer HRQOL for women.[43]

In terms of sociodemographic factors, women reported a lower educational attainment compared with men, which may make them more vulnerable in dealing with the many challenges that a diagnosis and management of PAD brings forth, potentially translating in poorer health status scores. Secondly, women were less likely to have a partner, which may decrease the 'protective effect' that marriage is equated with[48-49] owing to a lack of motivation for personnel care and/or a lack of social/moral support which may be detrimental to their health status. In particular, lack of social support has been shown to be a potent risk factor for women with CAD[50 51] due to a greater propensity to engage in unhealthy behaviors and thus may be an important factor on women's health status in this PAD cohort. While we did notice the presence of a more vulnerable socioeconomic profile in women, we were not able to confirm that these sociodemographics were responsible for the observed health status differences. These surrogate markers of socioeconomics (education, relationship status) should, however, definitely remain the focus of future research, as they have been able to explain many disparities in outcomes among cardiovascular populations.[50-52]

At initial diagnosis, women were also more likely than men to present with depressive symptoms, thus severely impacting their well-being. This finding has been previously demonstrated at diagnosis and long-term follow-up, specifically, younger women with PAD are known to be at a higher risk of depression than other gender-age groups.[17]

Depressive symptoms or 'mood states' as well as a greater degree of bodily pain may be associated with substantially compromised functional status[53] as well as a poorer prognosis,[54] which ultimately has adverse effects on patients' health status.[55, 56] We were only able to adjust for depression scores in the last step of our analyses, after including the most relevant demographic, socioeconomic, and clinical factors, and have not completed a formal mediation analysis, and as such, its explanatory role needs to be further explored in future work. At this time, we did not observe a dramatic change in the interpretation of the estimates for the association between female gender and health status after adjusting for patients' baseline depressive symptoms.

The adverse functional limitations experienced by women in this study are supported by the fact that women had a poorer pain-free walking distance and maximum walking distance and thus may have greater walking impairment from leg symptoms than men with PAD.[18,24, 25] Thus, the lower quality of life scores observed in women are not surprising given this greater compromise in walking ability. A poorer health status in women may then be directly affected due to restrictions in performing daily activities including grocery shopping and visiting family and friends.[26]

Mortality & adverse events

To complement our analyses on gender differences and health status outcomes in PAD, we additionally explored the association between gender, mortality and cardiovascular events. Cardiovascular mortality, all-cause mortality and major adverse coronary event rates by gender have not been well examined in PAD population-based studies. The few data available suggest that the relationship between ABI values, mortality (total, cardiovascular) and major coronary events are in fact similar between genders.[27] In the recent AHA statement, 16 population-based studies were pooled to examine these associations which revealed that the relationship between ABI values and total mortality, cardiovascular mortality, and major cardiovascular events are similar in women and men.[28] Furthermore, the gender effects on survival following lower-extremity PAD revascularization have been inconsistent[28] with some authors reporting a poorer long term survival in women[57] and others demonstrating improved survival[58] as compared with men.

In our study, with real-world patients recently diagnosed with PAD, we observed no significant gender differences in survival or experiencing a first adverse event over time, which seems to be in line with the indirect evidence that was derived from pooled population-based studies as described above. However, this appears to be counterintuitive with prior findings in CAD that provide clear evidence for poorer prognostic outcomes in women. Namely, women have a poorer 2-10 year long term survival rate following AMI compared with men.[13, 59, 60]

Limitations

Some limitations of this study are apparent. Firstly, only two institutions were included in this study and therefore results may only be generalizable to this type of setting. Secondly, although we adjusted for clinically important confounders in both the SF-12 regression models and Cox regression models, the possibility of residual confounding remains. Lastly, we did not utilize a disease-specific instrument and thus this should be the focus of future research.

CONCLUSION

In conclusion, this study has demonstrated for the first time in a prospective cohort of patients that were evaluated for their PAD in a specialty clinic that women's health status scores differ with scores from their male counterparts 12-months following the initial diagnosis of their PAD. We extended findings from earlier studies demonstrating that women suffer from more depressive symptoms and report a poorer physical and mental health status both at initial diagnosis (baseline) and 12-month follow-up.[20, 24-26, 43] Secondly, women seem to have a similar prognosis as examined for all-cause mortality or the experience of a first adverse event as compared with men. Future studies should focus on re-examining these effects using more sensitive disease-specific health status instruments and further exploring the role for socioeconomic, clinical, and psychological factors that may help explain these differences.

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APPENDIX 1 – The unadjusted and adjusted association between gender and baseline health status. Regression coefficients and 95% confidence intervals are presented.

	PCS12			MCS12		
	Estimate	**95% CI**	**P-value**	**Estimate**	**95% CI**	**P-value**
Unadjusted						
Female gender	**-2.76**	**-5.06;-0.46**	**.019**	-2.29	-4.98;0.40	.10
Adjusted step 1*						
Female gender	-2.25	-4.81;0.31	.09	**-2.95**	**-5.53;-0.37**	**.025**
Adjusted step 2†						
Female gender	9.83	-4.95;24.62	.19	-3.69	-19.40;12.01	.66
Adjusted step 3‡						
Female gender	-1.47	-4.00;1.06	.26	-0.40	-3.18;2.38	.79
Adjusted step 4§						
Female gender	**-2.70**	**-5.23;-0.16**	**.037**	-1.08	-3.45;1.29	.37
Adjusted step 5‖						
Female gender	**-2.17**	**-4.28;-0.06**	**.044**	-1.33	-3.22;0.56	.17
Adjusted step 6#						
Female gender	**-2.13**	**-4.17;-0.09**	**.041**	-1.78	-3.82;0.27	.09

The following covariates are sequentially included in the adjusted models: *adjusted model 1 = gender and age; †adjusted model 2 = model 1 and gender x age; ‡adjusted model 3 = model 1 and sociodemographics (no partner and <high school education); §adjusted model 4 = model 3 and clinical factors (diabetes, current smoking, prior stroke, prior myocardial infarction, heart failure, and renal dysfunction). The exploratory adjusted models include the following covariates: ‖exploratory adjusted model 5 = model 4 and depression; #exploratory adjusted model 6 = model 5 and co-morbidities (body mass index ≥30 kg/m², chronic obstructive pulmonary disease, back pain, and hip/knee osteoarthritis). Abbreviations: CI = confidence interval, MCS = mental component score, PCS = physical component score.

APPENDIX 2 – The unadjusted and adjusted association between gender and 12-month health status. Regression coefficients and 95% confidence intervals are presented.

	PCS12 at 12-months			MCS12 at 12-months		
	Estimate	**95% CI**	**P-value**	**Estimate**	**95% CI**	**P-value**
Unadjusted						
Female gender	**-3.89**	**-7.21;-0.58**	**.023**	**-4.66**	**-8.55;-0.77**	**.019**
Adjusted step 1*						
Female gender	**-3.90**	**-6.75;-1.06**	**.007**	**-4.99**	**-9.07;-0.91**	**.017**
Adjusted step 2†						
Female gender	-9.53	-30.03;10.97	.36	-17.30	-50.73;16.14	.31
Adjusted step 3‡						
Female gender	-2.32	-5.95;1.31	.22	-2.82	-6.75;1.11	.16
Adjusted step 4§						
Female gender	-3.41	-6.88;0.07	.057	**-4.10**	**-7.84;-0.36**	**.032**
Adjusted step 5‖						
Female gender	**-3.35**	**-6.34;-0.37**	**.028**	-2.21	-5.47;1.05	.19
Adjusted step 6#						
Female gender	-2.26	-5.05;0.54	.11	-2.44	-5.52;0.65	.12

The following covariates are sequentially included in the adjusted models: *adjusted model 1 = gender and age; †adjusted model 2 = model 1 and gender x age; ‡adjusted model 3 = model 1 and sociodemographics (no partner and <high school education); §adjusted model 4 = model 3 and clinical factors (diabetes, current smoking, prior stroke, prior myocardial infarction, heart failure, and renal dysfunction). The exploratory adjusted models include the following covariates: ‖exploratory adjusted model 5 = model 4 and depression; #exploratory adjusted model 6 = model 5 and co-morbidities (body mass index ≥30 kg/m², chronic obstructive pulmonary disease, back pain, and hip/knee osteoarthritis). Abbreviations: CI = confidence interval, MCS = mental component score, PCS = physical component score.

APPENDIX 3 – The unadjusted and adjusted association between gender and health status change scores. Regression coefficients and 95% confidence intervals are presented.

	PCS12 change scores			MCS12 change scores		
	Estimate	**95% CI**	**P-value**	**Estimate**	**95% CI**	**P-value**
Unadjusted						
Female gender	0.44	-1.66;2.54	.68	0.35	-1.69;2.39	.74
Adjusted step 1*						
Female gender	-0.74	-3.46;1.97	.59	0.26	-1.63;2.14	.79
Adjusted step 2†						
Female gender	-4.25	-21.22;12.72	.63	-9.57	-21.62;2.48	.12
Adjusted step 3‡						
Female gender	0.09	-2.85;3.03	.82	-0.77	-2.66;1.13	.44
Adjusted step 4§						
Female gender	-0.18	-2.44;2.08	.88	-0.78	-2.98;1.43	.49
Adjusted step 5‖						
Female gender	-0.16	-2.48;2.15	.89	-0.57	-2.79;1.65	.62
Adjusted step 6#						
Female gender	-0.53	-3.35;2.30	.71	0.30	-2.14;2.74	.81

The following covariates are sequentially included in the adjusted models: *adjusted model 1 = gender and age; †adjusted model 2 = model 1 and gender x age; ‡adjusted model 3 = model 1 and sociodemographics (no partner and <high school education); §adjusted model 4 = model 3 and clinical factors (diabetes, current smoking, prior stroke, prior myocardial infarction, heart failure, and renal dysfunction). The exploratory adjusted models include the following covariates: ‖exploratory adjusted model 5 = model 4 and depression; #exploratory adjusted model 6 = model 5 and co-morbidities (body mass index ≥30 kg/m², chronic obstructive pulmonary disease, back pain, and hip/knee osteoarthritis). Abbreviations: CI = confidence interval, MCS = mental component score, PCS = physical component score.

APPENDIX 4 - Full unadjusted and adjusted multivariate Cox Proportional regression model for mortality and all-cause adverse events (mortality, myocardial infarction, stroke, and lower-extremity amputation). Hazard ratios and 95% confidence intervals are presented.

	Mortality			Adverse events		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Unadjusted						
Female Gender	0.93	0.60;1.44	.74	0.90	0.63;1.29	.57
Adjusted 1						
Female Gender	0.90	0.58;1.39	.63	0.87	0.61;1.24	.43
Age	**1.05**	**1.03;1.08**	**<.001**	**1.06**	**1.04;1.08**	**<.001**
Adjusted 2						
Female Gender	0.86	0.55;1.34	.50	0.85	0.59;1.23	.39
Age	**1.05**	**1.02;1.08**	**<.001**	**1.06**	**1.04;1.08**	**<.001**
Diabetes	0.92	0.56;1.49	.72	0.98	0.67;1.45	.94
Current smoking	**1.57**	**1.00;2.45**	**.048**	**1.59**	**1.10;2.30**	**.013**
Prior stroke	0.74	0.32;1.72	.48	0.95	0.52;1.75	.87
Prior MI	1.30	0.81;2.10	.28	**1.72**	**1.18;2.52**	**.005**
Heart failure	**3.27**	**1.80;5.92**	**<.001**	**2.04**	**1.19;3.49**	**.010**
Renal dysfunction	**1.90**	**1.07;3.39**	**.030**	1.53	0.93;2.52	.10

Abbreviations: CI = confidence interval, HR = hazard ratio, MI = myocardial infarction.

APPENDIX 5 – Exploratory multivariable Cox proportional model for mortality and all-cause adverse events (death, myocardial infarction, stroke & amputation). Hazard ratios and 95% confidence intervals are presented.

	Mortality			Adverse events		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Unadjusted						
Female Gender	0.93	0.60;1.44	.74	0.90	0.63;1.29	.57
Adjusted 1						
Female Gender	0.90	0.58;1.39	.63	0.87	0.61;1.24	.43
Age	**1.05**	**1.03;1.08**	**<.001**	**1.06**	**1.04;1.08**	**<.001**
Adjusted 2						
Female Gender	0.86	0.55;1.34	.50	0.85	0.59;1.23	.39
Age	**1.05**	**1.02;1.08**	**<.001**	**1.06**	**1.04;1.08**	**<.001**
Diabetes	0.92	0.56;1.49	.72	0.98	0.67;1.45	.94
Current smoking	**1.57**	**1.00;2.45**	**.048**	**1.59**	**1.10;2.30**	**.013**
Prior stroke	0.74	0.32;1.72	.48	0.95	0.52;1.75	.87
Prior MI	1.30	0.81;2.10	.28	**1.72**	**1.18;2.52**	**.005**
Heart failure	**3.27**	**1.80;5.92**	**<.001**	**2.04**	**1.19;3.49**	**.010**
Renal dysfunction	**1.90**	**1.07;3.39**	**.030**	1.53	0.93;2.52	.10
Adjusted 3						
Female Gender	0.72	0.41;1.25	.24	0.70	0.45;1.10	.12
Age	**1.04**	**1.01;1.07**	**.004**	**1.06**	**1.03;1.08**	**<.001**
Diabetes	0.90	0.51;1.58	.72	0.99	0.63;1.55	.96
Current smoking	1.42	0.85;2.36	.18	**1.54**	**1.02;2.33**	**.041**
Prior stroke	0.93	0.40;2.20	.88	1.06	0.56;2.02	.85
Prior MI	1.22	0.69;2.15	.50	**1.56**	**1.01;2.43**	**.047**
Heart failure	**2.76**	**1.36;5.58**	**.005**	1.77	0.95;3.32	.07
Renal dysfunction	**2.03**	**1.06;3.88**	**.034**	1.58	0.90;2.77	.11
No partner	1.67	0.97;2.87	.06	1.55	0.90;2.77	.050
<High school education	1.12	0.66;1.88	.68	0.96	0.63;1.47	.86
Depression	1.60	0.97;2.63	.06	**1.60**	**1.06;2.41**	**.026**

Abbreviations: CI = confidence interval, HR = hazard ratio, MI = myocardial infarction.

Chapter 7

Determinants

of one-year depressive symptoms in patients with lower-extremity peripheral arterial disease

7

M. van Zitteren, K.G. Smolderen, P.W. Vriens, J. Denollet. Determinants of one-year depressive symptoms in patients with lower-extremity peripheral arterial disease. *Manuscript in preparation.*

ABSTRACT

***Background*:** Knowing what determinants are associated with depressive symptoms in patients with peripheral arterial disease (PAD) might help to timely adjust management of these symptoms. Therefore, we sought to explore determinants for the prevalence and persistence of depressive symptoms 1-year following PAD diagnosis.

***Methods and results*:** Between March 2006 and November 2011, 528 newly diagnosed PAD patients (Rutherford Grade I) were prospectively enrolled from 2 Dutch vascular clinics. Patients completed the Hospital Anxiety and Depression Scale to assess depressive symptoms (score ≥8) upon PAD diagnosis and at 1-year follow-up. A logistic regression analysis was used to evaluate the association of sociodemographic, clinical and psychological factors with depressive symptoms at follow-up. The model was replicated using a multinomial logistic regression analysis to assess determinants of 4 depression change categories, based on patients' depression scores at baseline and follow-up: (1) persistent; (2) new; (3) resolved; and (4) no symptoms of depression (reference). Lower education (OR=2.00, 95%CI 1.15-3.45, P=.014), diabetes mellitus (OR=2.24, 95%CI 1.28-3.94, P=.005), and the personality traits negative affectivity (OR=1.19, 95%CI 1.14-1.24, P<.0001) and social inhibition (OR=1.07, 95%CI 1.02-1.11, P=.004) were independently associated with 1-year depressive symptoms. Similar determinants were found for persistent depressive symptoms at 1-year follow-up.

***Conclusions*:** Educational level, medical comorbidity and personality are important determinants for the prevalence and persistence of depressive symptoms. Future studies should evaluate whether identification of depressed patients and subsequent depression treatment may help to reduce patients' health status burden.

INTRODUCTION

Patients with lower-extremity peripheral arterial disease (PAD) not only experience functional impairments due to a diminished lower-extremity arterial blood supply, but prior findings suggest that they are often confronted with a substantial psychological burden as well.[1-5] Depression, for example, has been widely reported in approximately one fifth (16-36%) of this vulnerable population.[6-14] In addition, the combination of having ischemic cardiovascular disease and depression is associated with adverse outcomes.[10, 11]

While depressive symptoms may compromise patients' long-term prognosis,[11] the immediate effects on their experienced PAD-related quality of life are substantial.[9, 11, 14] Addressing depressive symptoms in a timely fashion can actually help improve patients' depressive symptoms and quality of life.[12, 15] Yet, it is suggested that depressive symptoms in patients with PAD tend to persist over time.[8, 16, 17] This may be partially explained by the fact that in real-world clinical settings, the majority of depressive symptoms remain unrecognized leaving patients' psychological burden untreated.[18, 19] Other explanations for the persistence of patients' depressive symptoms could refer to the lack of information we have about important predictors of such symptoms that we failed to address in this population. Although few studies have evaluated persistence of depressive symptoms in PAD patients over time,[8, 12] they have not been widely replicated. Those studies found that persistent depressive symptoms are associated with a greater decline in functional status over time[12] and that depressed patients were more likely to use psychotropic medication and to be without a partner.[8] However, replication of these findings in recent PAD cohorts, and a better understanding of possible determinants of persistent depression are needed.

The present study therefore aimed to investigate the determinants of the prevalence and persistence of depressive symptoms in patients with PAD. Such knowledge may be helpful to identify patients who are at increased risk of (persistent) depression following their PAD diagnosis. Characterizing this subpopulation may be of help to improve the timely recognition and treatment of depressive symptoms.

METHODS

Study population and design

The present observational prospective study consisted of 528 consecutively enrolled patients with new onset symptoms of PAD or exacerbation of existing PAD for which patients were seeking treatment at 2 vascular surgery outpatient clinics (St. Elisabeth Hospital and TweeSteden Hospital, Tilburg, the Netherlands) between March 2006 and November 2011. Patients were eligible for inclusion if they had an abnormal ankle-brachial index upon rest (ABI≤0.90) or if their post-exercise ABI substantially decreased (≥15% from the resting ABI) following a distance limited (1000 meters) treadmill-walking test. Exclusion criteria were a non-compressible ABI (≥1.30), critical limb ischemia, severe cognitive impairment or severe somatic or psychiatric comorbidities (e.g., active oncology therapy or psychosis), illiteracy or insufficient knowledge of the Dutch language, or other reasons (e.g., treatment for PAD started before patients were able to complete self-report questionnaires). Because the present study focused on patients' self-reported 1-year depressive symptoms, patients were additionally excluded if the assessment of patients' depressive symptoms was not completed both at baseline and at 1-year following patients' diagnosis of PAD, thereby also excluding patients who died within 1-year follow-up.

All participants underwent a clinical evaluation by their treating vascular surgeon (i.e., thorough-history taking and physical examination) and vascular laboratory assessments (i.e., resting and post-exercise ABI assessments and a clinician-guided duplex ultrasound examination) upon enrollment. Patients completed self-reported questionnaires upon enrollment and 1-year following their PAD diagnosis to collect information on sociodemographics, self-reported depressive symptoms, and other psychological factors. Information on cardiovascular history, clinical factors and baseline medication use was abstracted from patients' medical records upon enrollment. One year following diagnosis, patients' medical records were searched again to document treatments (invasive vs. non-invasive management of their PAD symptoms).

The local ethics committee of each participating institution approved the study that was designed in line with the Helsinki Declaration. All participants provided written informed consent. Study participation did not influence treatment referral since the study was observational in nature.

MEASURES

Depressive symptoms

Patients' depressive symptoms were assessed with the Dutch version of the 14-item Hospital Anxiety and Depression Scale (HADS) questionnaire upon enrollment and 1-year following patients' PAD diagnosis. The HADS is a screening measure for detecting the presence of clinically relevant symptoms of depression and anxiety.[20] The presence of clinically relevant symptoms of depression was defined by a cut-off score of ≥8 on the depression subscale (HADS-D, range 0-21).[21] Mean change scores were calculated by subtracting patients' baseline scores from their 1-year scores. For our main analyses, patients were categorized in 1 of 4 depression categories based on their depression status (depressive vs. no depressive symptoms) at baseline and at 1-year follow-up:[12] (1) *persistent* depressive symptoms (both at baseline and follow-up); (2) *new* symptoms (no symptoms at baseline, but depressive symptoms at follow-up); (3) *resolved* symptoms (depressive symptoms at baseline but not at follow-up); and (4) *no* symptoms (reference group with no depressive symptoms at baseline and 1-year follow-up).

Ankle-brachial index assessments

Trained vascular technicians confirmed patients' PAD diagnosis using a handheld Doppler instrument (Imexlab 9000; Imex Medical Systems Inc, Golden Colorado) to assess their resting ABI as well as their post-exercise ABI following a distance-limited (1000 meters) treadmill-walking test. Per institutional protocol, patients' pain-free walking distance was also derived from the distance-limited treadmill-walking test. The diagnosis of PAD was confirmed if patients had a resting ABI ≤0.90[22, 23] or if a post-exercise decrease ≥15% was observed as compared with the resting ABI.[24]

The ABI was calculated by dividing the highest systolic ankle pressure in each leg (posterior tibial artery or dorsalis pedis artery) by the highest systolic brachial pressure.

Duplex ultrasound examination protocol

The Toshiba Xario ultrasound system (Xario XG; Toshiba Medical Systems Europe, Zoetermeer, the Netherlands) was used by trained vascular technicians to perform lower-extremity duplex ultrasound examinations as ordered by the patients' treating vascular surgeon as part of their diagnostic work-up. The protocol has been published in detail elsewhere.[25]

Information on lesion characteristics (i.e., anatomical lesion location, the number of lesions and lesion severity) was derived from duplex ultrasound readings. Lesions were considered significant when a peak systolic velocity (PSV [cm/sec]) ratio $\geq$2.5 or if a total occlusion (no flow, and no PSV ratio could be measured) was observed. A team of 3 physicians read all duplex ultrasounds prior to the study's analyses. Patients were categorized according to the anatomical lesion location that they presented with upon enrollment (i.e., proximal or distal lesions only, having both and distal lesions, or having non-significant lesions).

Treatment strategies

Information on the type of treatment that patients had received at the vascular specialty clinics between study enrollment and 1-year follow-up was documented through medical chart abstraction.[26] A detailed description of this protocol has been described previously.[26] Invasive options included any invasive lower-extremity procedure such as lower-extremity percutaneous transluminal angioplasty (PTA; with or without stent), endarterectomy, or bypass surgery. Non-invasive options included supervised exercise therapy, smoking-cessation counseling, and pharmacotherapy.

Clinical factors, comorbidities, and medical treatment

Information on cardiovascular risk factors, clinical factors, and comorbidities was obtained through medical chart abstraction and included: cardiac history (prior documented angina, myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, congestive heart failure), cerebrovascular history (prior documented stroke, transient ischemic attack), current smoking status, dyslipidemia, hypertension, body mass index (BMI, weight in kilograms divided by height in meters squared), chronic obstructive pulmonary disease (COPD), diabetes mellitus, renal dysfunction, back pain, and knee/hip osteoarthritis. Information on cardiovascular medication use following patients' vascular diagnostic evaluation was also collected through medical chart abstraction. Medication categories of interest included: aspirin, statin use, beta blockers, diuretics, angiontensin-converting enzyme (ACE) inhibitors, calcium antagonists, nitroglycerin, anti-coagulants, digoxin, and antiarrhythmics.

Sociodemographic factors

Patients' medical records were searched to obtain demographic information (age, sex) and purpose-designed questionnaires were administered to obtain information on socioeconomic factors (marital status [no partner vs. partner], educational background [lower education vs. high school education or more], and work status [active vs. non-active work status]) upon enrollment.

Psychological Factors

Personality Assessment

The DS14 scale was used to assess the personality traits negative affectivity (i.e., the tendency to experience negative emotions) and social inhibition (i.e., the tendency to inhibit self-expression) as determinants of (change in) 1-year depressive symptoms.[27] The combination of these traits (score $\geq$10 on both traits) in the Type D personality construct[27] has previously been associated with the onset and persistence of depressive symptoms[17, 28] and adverse events[17, 28-30] in cardiac populations. Therefore, we additionally explored the Type D construct as a potential determinant of depressive symptoms in the present study.

Psychological Counseling and Psychopharmacological Drugs

Upon enrollment, self-reported information on psychological counseling was also captured to determine whether patients were currently being seen by a social worker, psychologist, or psychiatrist for their psychological problems. Information on the use of psychopharmacological drugs was abstracted from patients' medical records at baseline and included antidepressants, anxiolytics, and hypnotics.

Statistical analysis

Patients' baseline characteristics and psychological characteristics were described for the total population and compared by patients' self-reported baseline depressive symptoms (HADS depression scores ≥8 vs. scores <8) using the Chi-Squared test, Fishers' Exact test, Students' t-test or Wilcoxon Rank Sum test as appropriate. Scores of depressive symptoms (at baseline, at 1-year follow-up and change scores) were also compared by the 4 categories of 1-year change in depressive symptoms (persistent, new, resolved, no depressive symptoms) using one-way ANOVA (analysis of variance) and the Kruskal Wallis test.

A logistic regression model was constructed to identify determinants of 1-year depressive symptoms using the following categories: (1) depressive symptoms at follow-up (i.e., persistent and new symptoms) *versus* (2) no depressive symptoms at follow-up (i.e., resolved and no symptoms). The model was sequentially built using the following steps: (1) demographics (age, sex); (2) marital status (no partner vs. partner), educational background (lower education vs. high school education); (3) patients' lowest resting ABI, and 1-year invasive treatment (invasive vs. non-invasive treatment); (4) angina, BMI, current smoking, diabetes mellitus, renal dysfunction, and back pain; and (5) the continuous subscales of (a) negative affectivity and (b) social inhibition. The interaction term between negative affectivity and social inhibition was also tested in a logistic regression model where depressive vs. no depressive symptoms at 1-year follow-up served as dependent variable, but was not significant (P=.11) and therefore not included in the models.

Likewise, a multinomial logistic regression model was performed as exploratory analysis to search for determinants of persistence of 1-year depressive symptoms using the 4 depression categories of persistent, new, resolved and no depressive symptoms. Finally, for reasons of interpretability, the logistic and multinomial logistic regression models were replicated where the last step of the adjusted model (negative affectivity and social inhibition) was replaced by Type D personality as dichotomous variable (yes vs. no) to investigate the combined effect of negative affectivity and social inhibition as a potential indicator of depressive symptoms.

Patients with depression scores at baseline and 1-year follow-up were included, and a complete case analysis was performed (0.2-1.9% missing values for covariates). PASW Statistics 19.0 for Windows (SPSS inc. Chicago, IL) was used to execute all analyses. All tests were two-tailed and P-values <.05 were considered statistically significant.

RESULTS

Baseline characteristics

Patients' baseline characteristics are presented in Table 1 for the total population (n=528) and by the presence of depressive symptoms (depressive vs. no depressive symptoms) upon PAD diagnosis. The mean age of the overall population was 65.5 years (±9.4 years) and 67% was male.

Patients having significant depressive symptoms upon PAD diagnosis (n=138; 26%) presented with a lower educational status, diabetes mellitus, back pain, and had a shorter pain-free walking distance as compared with patients without such symptoms. No differences were observed in cardiovascular history, lower-extremity revascularization, anatomical lesion location or cardiovascular medication use (Table 1). Furthermore, those having depressive symptoms upon PAD diagnosis had higher levels of negative affectivity, social inhibition, and had a higher proportion of patients that classified for a Type D personality, patients that were in need of psychological counseling, and that were on antidepressants or anxiolytics as compared with those without depressive symptoms (Table 1). Patients presenting with lower baseline scores of depressive symptoms also reported lower scores at 1-year follow-up, while patients having higher baseline scores of depressive symptoms had higher scores at 1-year follow-up (Pearson r=0.71, 95%CI 0.66-0.75, P<.05).

Depression categories

Table 2 presents scores of depressive symptoms for the 4 depression categories. A total of 94 (18%) patients had persistent depressive symptoms; 42 (8%) patients developed new depressive symptoms over time; in 44 (8%) patients, the initial depressive symptoms resolved over time; and 348 (66%) patients did not report depressive symptoms both upon diagnosis and at 1-year follow-up. Median depression scores (±SD) upon PAD diagnosis ranged from 3.0±2.0 to 10.0±2.8 across the 4 depression categories, and were highest in those who had persistent symptoms of depression.

Median 1-year depression scores ranged from 3.0±2.1 to 11.01±2.9 across these categories, and were highest among those with persistent depressive symptoms. Change scores ranged between -4.4±2.0 and +4.6±3.2; patients with new symptoms had the largest change (increase of +4.6±3.2 points).

Table 1 - Baseline characteristics of the total sample and stratified by depressive symptoms at baseline.

	Total sample (n = 528)	Depressive symptoms (n = 138)	No depressive symptoms (n = 390)	P-value
Demographics				
Age, mean (SD) years	65.5 (9.4)	64.2 (9.6)	66.0 (9.3)	.055
Male sex, n (%)	354 (67.0)	84 (60.9)	270 (69.2)	.07
Socioeconomic factors				
No partner, n (%)	123 (23.3)	39 (28.3)	84 (21.6)	.11
Lower education, n (%)	**128 (24.4)**	**44 (32.6)**	**84 (21.6)**	**.010**
Working full- or part time, n (%)	128 (25.0)	29 (22.5)	99 (25.8)	.45
Cardiovascular history				
Angina pectoris, n (%)	70 (13.3)	16 (11.6)	54 (13.8)	.50
Myocardial infarction, n (%)	96 (18.2)	29 (21.0)	67 (17.2)	.32
CABG, n (%)	62 (11.7)	19 (13.8)	43 (11.0)	.39
PCI, n (%)	49 (9.3)	14 (10.1)	35 (9.0)	.68
Congestive heart failure, n (%)	24 (4.5)	8 (5.8)	16 (4.1)	.41
Stroke, n (%)	48 (9.1)	16 (11.6)	32 (8.2)	.23
TIA, n (%)	51 (9.7)	12 (8.7)	39 (10.0)	.66
Clinical factors				
Smoking, n (%)	248 (47.0)	71 (51.4)	177 (45.5)	.22
Hypercholesterolemia, n (%)	358 (67.8)	97 (70.3)	261 (66.9)	.47
Hypertension, n (%)	322 (61.0)	85 (61.6)	237 (60.8)	.86
BMI, mean (SD)	26.9 (5.2)	27.1 (6.7)	26.8 (4.6)	.70

	Total sample (n = 528)	Depressive symptoms (n = 138)	No depressive symptoms (n = 390)	P-value
Table 1 (Continued)				
Comorbidities				
COPD, n (%)	85 (16.1)	29 (21.0)	56 (14.4)	.07
Diabetes mellitus, n (%)	**121 (22.9)**	**43 (31.2)**	**78 (20.0)**	**.007**
Renal dysfunction, n (%)	51 (9.7)	14 (10.1)	37 (9.5)	.82
Back pain, n (%)	**82 (15.5)**	**31 (22.5)**	**51 (13.1)**	**.009**
Hip or knee osteoarthritis, n (%)	112 (21.2)	29 (21.0)	83 (21.3)	.95
Vascular laboratory assessment				
PFWD, median (SD), m	**80.0 (145.1)**	**70.0 (113.6)**	**80.0 (154.3)**	**.045**
Resting ABI, mean (SD)*	65.9 (16.4)	67.6 (17.2)	65.3 (16.0)	.17
Lower-extremity revascularization				
Prior endovascular, n (%)	70 (13.3)	21 (15.2)	49 (12.6)	.43
Prior surgery, n (%)	36 (6.8)	11 (8.0)	25 (6.4)	.53
≤1-year following diagnosis, n (%)	192 (36.4)	56 (40.6)	136 (34.9)	.23
Anatomical lesion location				.59
Proximal, n (%)	135 (28.4)	41 (31.5)	94 (27.2)	
Distal, n (%)	254 (53.4)	63 (48.5)	191 (55.2)	
Proximal and distal, n (%)	43 (9.0)	12 (9.2)	31 (9.0)	
Non-significant, n (%)	44 (9.2)	14 (10.8)	30 (8.7)	
Medication use				
Aspirin, n (%)	407 (77.1)	106 (76.8)	301 (77.2)	.93
Anticoagulants, n (%)	84 (15.9)	23 (16.7)	61 (15.6)	.78

	Total sample (n = 528)	Depressive symptoms (n = 138)	No depressive symptoms (n = 390)	P-value
Table 1 (Continued)				
Statins, n (%)	434 (82.2)	115 (83.3)	319 (81.8)	.69
Beta blocker, n (%)	221 (41.9)	59 (42.8)	162 (41.5)	.80
Diuretics, n (%)	131 (24.8)	35 (25.4)	96 (24.6)	.86
ACE inhibitor, n (%)	175 (33.1)	48 (34.8)	127 (32.6)	.63
Calcium antagonist, n (%)	119 (22.5)	32 (23.2)	87 (22.3)	.83
Nitroglycerin, n (%)	46 (8.7)	15 (10.9)	31 (7.9)	.30
Digoxin, n (%)	11 (2.1)	1 (0.7)	11 (2.6)	.17
Antiarrhythmics, n (%)	13 (2.5)	3 (2.2)	10 (2.6)	.80
Psychological factors				
Negative affectivity score, mean (SD)	**7.9 (6.2)**	**13.1 (6.2)**	**6.0 (5.0)**	**<.0001**
Social inhibition score, mean (SD)	**8.9 (6.0)**	**12.1 (6.3)**	**7.7 (5.4)**	**<.0001**
Type D personality, n (%)	**113 (21.6)**	**68 (49.6)**	**45 (11.6)**	**<.0001**
Psychosocial assistance, n (%)	**17 (3.3)**	**13 (9.5)**	**4 (1.0)**	**<.0001**
Psychopharmacological drug use				
Antidepressants, n (%)	**30 (5.7)**	**20 (14.5)**	**10 (2.6)**	**<.0001**
Anxiolytics, n (%)	**22 (4.2)**	**11 (8.0)**	**11 (2.8)**	**.009**
Hypnotics, n (%)	23 (4.4)	8 (5.8)	15 (3.8)	.34

Abbreviations: SD = standard deviation; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention, TIA = transient ischemic attack; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ACE inhibitor = angiotensin-converting-enzyme inhibitor; PFWD = pain-free walking distance; ABI = ankle-brachial index; *lowest ABI measured.

Table 2 –Scores of depressive symptoms by 1-year depression change categories.

	Category 1 Persistent (n = 94)	Category 2 New (n = 42)	Category 3 Resolved (n = 44)	Category 4 No depression (n = 348)	P-value*
HADS Depression scores					
Baseline scores, median (SD)	**10.0 (2.8)**	**5.2 (1.9)**	**9.0 (1.2)**	**3.0 (2.0)**	**<.0001**
1-year scores, median (SD)	**11.0 (2.9)**	**9.0 (2.1)**	**5.0 (1.9)**	**3.0 (2.1)**	**<.0001**
Change scores, mean (SD)	**+0.57 (2.6)**	**+4.6 (3.2)**	**-4.4 (2.0)**	**-0.21 (2.1)**	**<.0001**

Category 1 (persistent) = Depressive symptoms at baseline and 1-year follow-up; Category 2 (new) = no depressive symptoms at baseline, but depressive symptoms at 1-year follow-up; Category 3 (resolved) = depressive symptoms at baseline but not at 1-year follow-up; Category 4 (no depression) = no depressive symptoms at baseline and 1-year follow-up. Abbreviations: SD = standard deviation; *P-value for trend.

Determinants of 1-year depressive symptoms

In the logistic regression model, lower education (OR=2.00, 95%CI 1.15-3.45, P=.014), diabetes mellitus (OR=2.24, 95%CI 1.28-3.94, P=.005) negative affectivity (OR=1.19, 95%CI 1.14-1.24, P<.0001) and social inhibition (OR=1.07, 95%CI 1.02-1.11, P=.004) were independently associated with depressive symptoms at 1-year follow-up (See Table 3 for full model results). Similar determinants were observed when exploring the joint tendency of negative affectivity and social inhibition in the Type D construct, where Type D (OR=6.01, 95%CI 3.70-9.76, P<.0001) also served as an independent predictor of 1-year depressive symptoms (Figure). This may be explained by the high prevalence of Type D personality (49%) in depressed patients as compared to those without depression (12%).

Determinants of 1-year depression change categories

Having a lower educational status (OR=2.50, 95%CI 1.26-4.97, P=.009), diabetes mellitus (OR=3.27, 95%CI 1.60-6.67, P=.001), back pain (OR=2.49, 95%CI 1.14-5.44, P=.022), negative affectivity (OR=1.30, 95%CI 1.22-1.37, P<.0001) and social inhibition (OR=1.09, 95%CI 1.03-1.15, P=.002) were all factors that were independently associated with persistence of depressive symptoms over time.

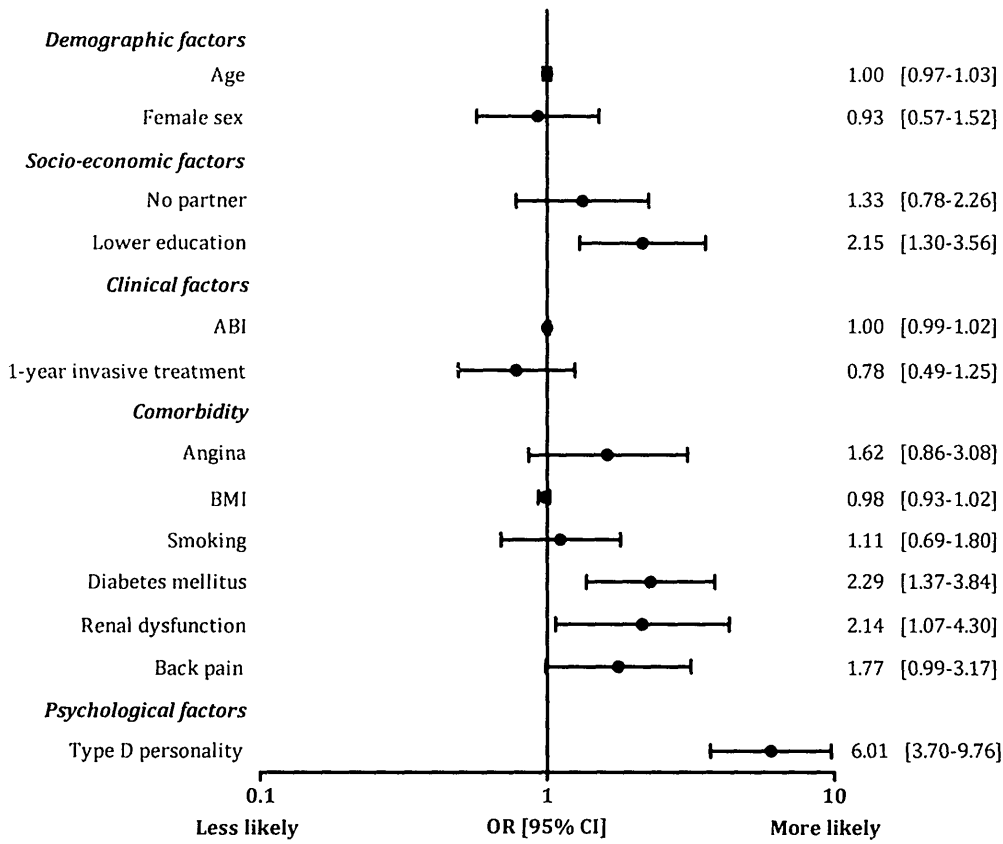
Furthermore, negative affectivity was also a determinant in patients with resolved depressive symptoms (OR=1.16, 95%CI 1.09-1.23, P<.0001), and in patients who developed new symptoms of depression during follow-up (OR=1.12, 95%CI 1.05-1.20, P<.0001). A non-significant trend was observed for the association between non-invasive treatment of PAD and the development of depressive symptoms (OR=0.45, 95%CI 0.20-1.03, P=.058). Full model results are presented in the Appendix. No other determinants were observed when replicating the model with Type D personality as final adjusted step.

Table 3 – Full logistic regression model results for determinants for 1-year depression status (depressed [HADS depression score ≥8] vs. not depressed [HADS depression score <8]). Odds Ratios [OR] and their 95% Confidence intervals [CI] are presented.

	OR (95%CI)	P-value
Age	1.01 (0.98-1.04)	0.71
Female Sex	0.83 (0.47-1.42)	.49
No partner	1.41 (0.78-2.53)	.25
Lower education	**2.00 (1.15-3.45)**	**.014**
Lowest resting ABI	1.00 (0.99-1.02)	.76
1-year invasive treatment	0.86 (0.52-1.44)	.57
Angina	1.42 (0.72-2.81)	.31
BMI (kg/m^2)	1.00 (0.95-1.05)	.90
Smoking	1.22 (0.72-2.05)	.47
Diabetes mellitus	**2.24 (1.28-3.94)**	**.005**
Renal dysfunction	1.58 (0.75-3.37)	.23
Back pain	1.73 (0.92-3.23)	.09
Negative affectivity*	**1.19 (1.14-1.24)**	**<.0001**
Social inhibition*	**1.07 (1.02-1.11)**	**.004**

Abbreviations: ABI = ankle-brachial index; BMI (body mass index in kilograms divided by height in meters squared); CI = confidence interval; OR = Odds Ratio. *Continuous scores, risk is associated with 1 point increase in scale score (range 0-28).

Figure - Forest plot of full logistic regression model results of determinants of 1-year depressive symptoms with Type D personality (depressive vs. no depressive symptoms). Odds Ratios [OR] and their 95% Confidence intervals [CI] are presented.



Abbreviations: ABI = ankle-brachial index; BMI (body mass index in kg/m^2); CI = confidence interval; Type D = distressed personality defined by the combination of negative affectivity and social inhibition; OR = Odds Ratio.

DISCUSSION

This study identified several determinants of persistent and new depressive symptoms in patients with newly diagnosed PAD. About a quarter of patients had depressive symptoms upon enrollment to the study, and these patients were often burdened by medical comorbidities such as diabetes mellitus and back pain. Of note, 18% of PAD patients had persistent depressive symptoms, and an additional 8% of patients developed new depression symptoms over time. Lower educational status, diabetes mellitus, and the personality traits negative affectivity and social inhibition were independently associated with depressive symptoms at 1-year follow-up. These factors were also independently associated with persistence of depressive symptoms over time. Finally, negative affectivity was associated with change in patients' depressive symptoms over time.

Given the documented burden of depression that exists in a great proportion of the PAD population,[6-8, 31, 32] and because few studies have evaluated persistence of depressive symptoms over time,[8, 12] there is a real need to understand what factors are related to the presence and persistence of depressive symptoms in patients with PAD. Inspired by prior PAD research on depression determinants,[8, 12] this study aimed to replicate and extend prior findings of determinants that are associated with the presence and persistence of depression in patients with PAD in the following ways: The population under study was a relatively large sample of a homogenous cohort of patients with new onset symptoms of PAD that was prospectively evaluated. In addition to the prevalence of depressive symptoms at 1-year follow-up, this study also evaluated the persistence and onset of depressive symptoms over time as valuable replication of prior work.[8, 12] Not only did we have a wide variety of baseline patient characteristics and medical data available, but we could complement this information with 1-year treatment referral that might have affected patients' psychological well-being. This rich data made it possible to extensively explore sociodemographic, medical and psychological factors as possible determinants for presence and persistence of depressive symptoms over time.

In line with prior findings from PAD cohorts,[8, 32] we found that patients with a lower educational status had more depressive symptoms. These patients might have limited access to (interventional) treatment options, and might experience an increased socioeconomic burden on top of their chronic disease burden. Consistent with previous research,[8, 31, 33-35] diabetes mellitus and back pain were also important medical correlates of depressive symptoms. Depression in PAD patients has been associated with greater functional decline or less improvement in health status over time as compared with non-depressed PAD patients.[7, 9, 12] Our findings suggest that these PAD-related functional impairments may be further amplified by the chronic burden of concomitant comorbidities. Finally, the personality traits negative affectivity and social inhibition, and their combination in Type D patients, were major determinants for the prevalence and persistence of depressive symptoms.[36] In previous research, Type D personality has been associated with an increased risk of depression in cardiac and general populations.[35, 37, 38] In our study, Type D was present in nearly half of the depressed patients vs. only 12% in patients without depression.

In addition to focusing on patients' medical condition, clinicians should be aware that a quarter of PAD patients may present with underlying depressive symptoms. Importantly, a substantial proportion of patients with PAD and coexisting depression will not be recognized as such. There is an ongoing debate as to whether routine screening for the presence of depressive symptoms in cardiovascular disease patients is recommended.[18, 19, 39-43] For patients with coronary artery disease, the American Heart Association published a scientific statement to incorporate a two-step depression screening tool in current treatment guidelines.[40] Identification and treatment of depressive symptoms has the potential to improve patients' depression[44] and impaired health status,[45] provided that institutional infrastructures such as the availability of a depression case manager, and collaborative care networks are in place.[46, 47]

Whether identification and subsequent treatment of depression in PAD patients may improve patients' quality of life, PAD-related symptoms and prognosis has not been evaluated. A first step might be creating awareness - among health care providers - of the depression burden in patients with PAD and by the early identification of patients who are at increased risk for depressive symptoms in the clinical setting. Regardless of the question whether subsequent treatment for depression will be beneficial for patients' PAD-related burden and prognosis, it is important to note that depression in itself, deserves to be treated in its own right. To facilitate this, specialty clinics should find ways to collaborate with primary care providers to optimize treatment strategies for patients' depression burden (e.g., extensive monitoring of patients' depression status) in addition to the usual care.

This study should be interpreted against the following limitations. The use of a self-report measure might have led to a greater proportion of patients being classified as having depressive symptoms as compared with the diagnosis of depression with a standardized psychiatric interview. Furthermore, our results may only be generalizable to Dutch population settings due to possible differences in reimbursement rates for and access to supervised exercise programs that may be different in other settings. Finally, we cannot exclude the possibility of residual confounding despite adjusting for important confounding factors in predicting depressive symptoms over time.

CONCLUSIONS

The present study confirmed that depressive symptoms are present in a substantial proportion of a PAD population seen in vascular specialty clinics. Moreover, the majority of patients who presented with depressive symptoms at initial PAD diagnosis also tended to have stable depressive symptoms over time, and an additional proportion may develop new depressive symptoms over time. Clinicians should be aware that lower educational status, diabetes mellitus and Type D personality traits are important determinants of depressive symptoms. Future research efforts in PAD should evaluate whether screening tools can adequately identify depression in clinical settings, and facilitate its treatment.

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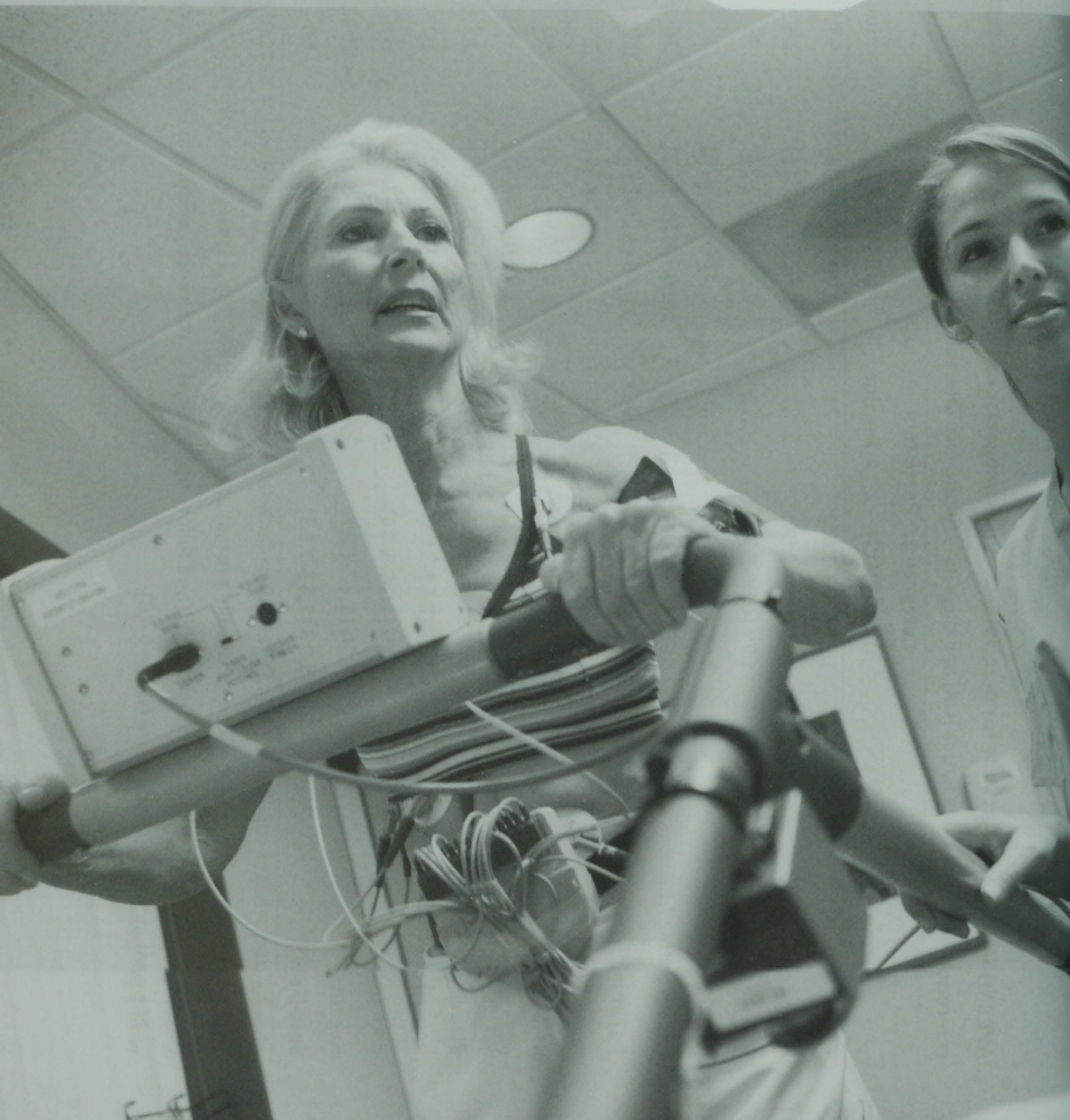
APPENDIX – Full model results for determinants for 4 categories of 1-year change in depressive symptoms (with no depressive symptoms as reference category). Odds Ratios [OR] and their 95% Confidence intervals [CI] are presented.

	Category 1:* Persistent		Category 2:† New		Category 3:‡ Resolved	
	OR (95%CI)	**P-value**	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**
Age	1.01 (0.97-1.05)	.71	1.00 (0.96-1.04)	.93	0.99 (0.95-1.03)	.59
Female Sex	0.95 (0.49-1.84)	.87	0.63 (0.28-1.44)	.28	0.97 (0.45-2.05)	.93
No partner	1.79 (0.86-3.72)	.12	0.92 (0.37-2.24)	.85	1.00 (0.41-2.45)	.99
Lower education	**2.50** (1.26-4.97)	**.009**	1.45 (0.65-3.26)	.37	0.90 (0.37-2.19)	.81
Lowest resting ABI	1.02 (1.00-1.04)	.15	0.98 (0.96-1.01)	.16	1.00 (0.98-1.02)	.94
1-year invasive treatment	1.27 (0.67-2.41)	.46	0.45 (0.20-1.03)	.058	1.07 (0.52-2.22)	.85
Angina	1.12 (0.46-2.70)	.81	1.65 (0.68-3.97)	.27	0.65 (0.18-2.33)	.50
BMI (kg/m^2)	1.00 (0.93-1.06)	.90	1.03 (0.96-1.10)	.40	1.05 (0.99-1.11)	.13
Smoking	1.67 (0.86-3.24)	.13	1.00 (0.47-2.12)	.99	1.60 (0.76-3.38)	.22
Diabetes mellitus	**3.27 (1.60-6.67)**	**.001**	1.83 (0.84-4.02)	.13	1.71 (0.73-3.99)	.21
Renal dysfunction	1.37 (0.53-3.55)	.52	1.32 (0.48-3.62)	.60	0.21 (0.03-1.65)	.14
Back pain	**2.49 (1.14-5.44)**	**.022**	1.27 (0.74-3.41)	.64	1.95 (0.79-4.83)	.15
Negative affectivity§	**1.30 (1.22-1.37)**	**<.0001**	**1.12 (1.05-1.20)**	**<.0001**	**1.16 (1.09-1.23)**	**<.0001**
Social inhibition§	**1.09 (1.03-1.15)**	**.002**	1.06 (0.99-1.12)	.08	1.07 (1.00-1.14)	.052

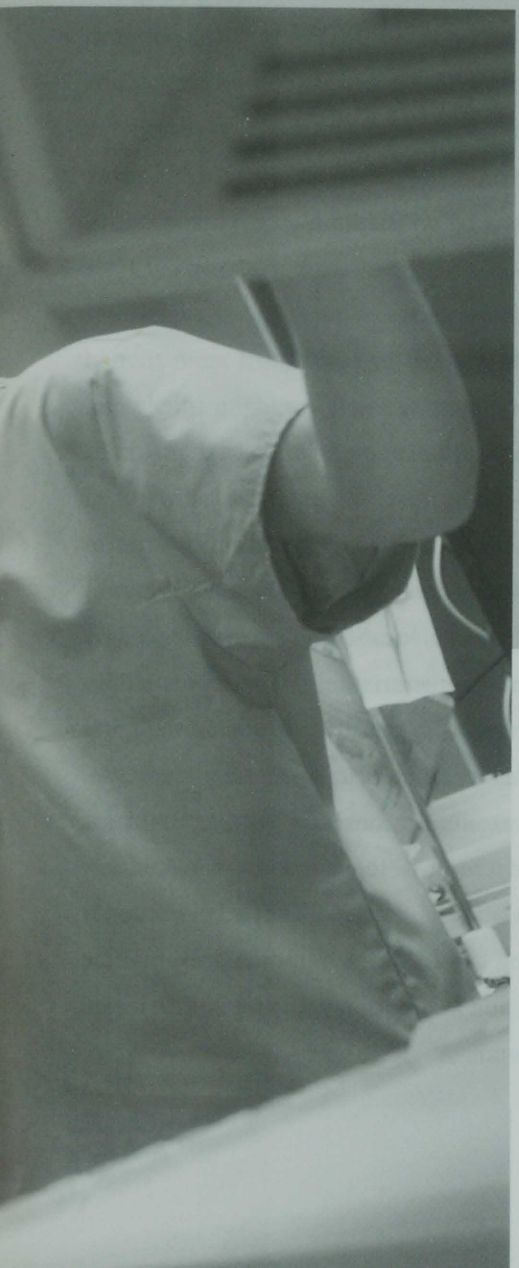
Abbreviations: ABI = ankle-brachial index; BMI = body mass index. *Category 1 (persistent) = depressive symptoms at baseline and follow-up; ‡Category 2 (new) = depressive symptoms only present at follow-up; †Category 3 (resolved) = depressive symptoms were resolved at follow-up. The category "no depressive symptoms at baseline and follow-up" severed as reference category in all comparisons. §Continuous scores, risk is associated with 1 point increase in scale score (range 0-28).

Chapter 8



Discussion

8



Patients with lower-extremity peripheral arterial disease (PAD) are undertreated. The rationale of this thesis is based on the observation that the identification of subpopulations, risk stratification initiatives, and the documentation of the clinical-decision making process and patient-centered outcomes is underexposed in the field of PAD as compared with research that has been conducted in cardiac populations. Given these identified gaps in the current knowledge of PAD, this thesis aims to cover three major topics to advance the field of PAD. Firstly it focuses on the identification of subpopulations in PAD in terms of arterial lesion characteristics, leg symptom presentation, self-reported health status, gender-related differences, and change in depressive symptoms in patients with lower-extremity PAD. Second, the clinical-decision making process for invasive treatment referral in patients with PAD is examined. Furthermore, (patient-centered) outcomes are documented in greater detail for the identified subpopulations. Finally, recommendations for future research directions and clinical implications are provided based on the findings reported in this thesis.

8.1. What is known from previous research?

8.1.1. Existing knowledge on subpopulations in peripheral arterial disease

Based on anatomic lesion location

The distribution of atherosclerotic plaque formation in the lower-extremity arteries varies according to the anatomical segment.[1-6] Previous research has additionally demonstrated that patients presenting with different locations of lower-extremity arterial lesions differ with respect to their clinical characteristics.[1-6] There is evidence that patients' risk for cardiovascular events might vary due to different etiological mechanisms.[6, 7] Although contrary findings have been reported, it is generally found that patients presenting with proximal lesions (i.e., aortoiliac lesions) are younger smokers, whereas distal lesions (i.e., femoropopliteal and crural lesions) are more commonly found in the elderly presenting with diabetes.[2-4, 6, 7] Despite these efforts, the broader spectrum of patients' characteristics, including their leg symptom presentation, cardiovascular risk profile, psychological aspects, and association with anatomical lesion location has not yet been characterized in great detail.

Documenting such information (*Chapter 2*) might provide novel insights in determining distinct patient profiles to facilitate more tailor-made treatment strategies for PAD.

Subpopulations based on pre-procedural health status

The main goals of PAD management are to improve patients' health status, to reduce their symptoms, and to prevent future adverse events.[8-10] Yet, research has mostly focused on documenting patency rates in interventional cohorts,[11-13] but the assessment of patients' health status (benefits) has received little attention. Prior studies demonstrated that patients indeed reported improved health status scores after undergoing successful endovascular procedures.[14-18] Although these studies have compared pre-procedural health status scores with health status during follow-up, they were mostly unable to compare patients undergoing invasive vs. non-invasive treatment strategies. Furthermore, despite documenting the health status burden in patients with PAD, no studies have specifically focused on the identification of subpopulations by stratifying patients according to their pre-procedural self-reported health status. Therefore, little is known about which subpopulations of PAD patients will eventually benefit most from invasive vs. non-invasive treatment referral. Evaluating this gap in knowledge might provide meaningful information to both clinicians and patients to help them making a decision on their treatment. *Chapter 5* aims to provide insights in characteristics of patients' self-reported pre-procedural health status.

Gender-related differences in peripheral arterial disease

Although prior research has observed gender-related disparities in outcomes in cardiac patients, these differences remain under documented in PAD.[19-22] Therefore, the recently launched statement of the American Heart Association recommends carefully documenting gender differences in PAD patients as this information could potentially contribute to the understanding as to how we can tailor treatment better to patients' needs.[23] As a next step, *Chapter 6* evaluates gender-related differences in patient characteristics in those with newly diagnosed PAD.

Subpopulations in the depression burden of peripheral arterial disease

Patients with PAD not only experience functional impairments,[8, 9, 14, 15, 17, 18, 24-27] but they often experience a substantial comorbid psychological burden.[27-30] Depression, for example, has been associated with a comprised health status and adverse events in cardiovascular populations,[27, 31-34] and is approximately present in 20% (16-36%) of patients with PAD.[27-29, 31, 35-38] Despite the prior documented disease burden of depression in patients with PAD, it has received little attention in PAD management (e.g., referral for psychological interventions). Although depressive symptoms are generally stable,[35, 39, 40] some patients experience a change in their depressive symptoms over time.[41-43] It remains unclear, however, which patients will eventually experience a change in depressive symptoms over time. As a first step to identify subpopulations in terms of depressive symptoms, *Chapter 7* explores what patient profile is associated with depressive symptoms following patients' initial PAD diagnosis.

8.1.2. Existing knowledge on the quality of the clinical decision-making process

After a diagnosis of PAD, some physicians still let themselves guide by the anatomical lesion location to refer patients for invasive treatment in accordance with existing guidelines.[8-10] However, it is generally recommended to offer patients with PAD (Fontaine 2) non-invasive treatment strategies first before proceeding to invasive procedures.[8-10] Moreover, the presence of focal aortoiliac disease appears to be an indication for more prone invasive treatment.[8, 9]

While various factors – including lesion characteristics, functional impairments, and insufficient benefits from non-invasive treatment – are mentioned by PAD guidelines to take into account when referring patients for a certain treatment strategy,[8-10] it remains unclear how these factors are actually being valued in the clinical decision-making process in real world clinical practices. In addition, it remains unclear how clinical-decision making processes differ across institutions. Prior research already indicated that such provider variation in care exists – albeit documented in patients from the United States with critical limb ischemia[44, 45] – but efforts to quantify this variation in care have been scarce in Europe and in patients with earlier stages of the disease.

Hence, *Chapter 3* explores determinants for invasive vs. non-invasive treatment referral within the first year after patients' initial PAD diagnosis, and additionally explores treatment variations in 2 vascular outpatient institutions. Irrespective of the observed treatment variations,[44-46] the present guidelines state that relieving patients' symptoms of PAD and improving their health status are the main goals of PAD treatment.[8-10, 47]

8.1.3. Outcomes in peripheral arterial disease

Multiple cardiovascular events

Another goal of PAD management is the prevention of future adverse events. Prior prognostic studies in PAD mainly focused on hard endpoints such as hemodynamic success rates,[11-13] non-fatal cardiovascular events, and mortality.[48, 49] They demonstrated that PAD is generally associated with an excessive risk of adverse cardiovascular events (e.g., myocardial infarction, stroke, transient ischemic attack, lower-extremity amputation) and mortality.[48, 49] The REACH Registry, for example, demonstrated that polyvascular disease (i.e., coronary artery disease, carotid disease, and PAD) is associated with a poorer prognosis as compared with those having a single arterial bed affected.[48, 49]

One recent study evaluated the role of proximal vs. distal lower-extremity lesions in PAD, and found a poorer prognosis in patients with proximal vs. distal PAD.[7] In terms of extensiveness of lower-extremity lesions (i.e., the number of lesions) only one older study (1985) reported that patients presenting with multiple lower-extremity lesions had a lower 6-year survival as compared with those having a single lower-extremity lesion.[50]

Despite these efforts, the relationship between lesion characteristics (i.e., anatomical location and extensiveness) and cardiovascular outcomes remains underexposed in the field of PAD. One major limitation of previous PAD research includes the fact that all studies focused on the occurrence of one adverse event and none has ever evaluated the occurrence of multiple adverse events over time in PAD patients. Therefore, *Chapter 4* thoroughly studies the association between the presence of multiple lower-extremity lesions and patients' risk for experiencing a first as well as multiple cardiovascular events over time.

Change in health status following diagnosis and treatment of peripheral arterial disease

Since PAD is also associated with a psychological burden,[27-30] it would be appropriate to not only document hard endpoints such as adverse events and mortality, but to complement this information with patient-centered outcomes as well. Although such studies are limited, preliminary findings from cardiac populations suggest that patients with a poorer health status have increased risks of hospitalizations and mortality as compared with those having better health status scores.[14, 51-54] In patients seen in vascular specialty clinics, it is unknown, however, if their health status changes over time after referral for invasive vs. non-invasive treatment strategies. *Chapter 5* explores the change in patients' 1-year self-reported health status by invasive treatment referral.

The woman's position in health status and outcomes

In coronary artery disease populations, women were at increased risk of reporting a poorer health status[55] and for in-hospital, long-term[20-22] and post-procedural mortality.[19, 56] Although differences have been reported in the prevalence of PAD between men and women,[23] knowledge on gender-related differences in health status and outcomes remains underexposed. The preliminary work in PAD demonstrated that women are indeed at increased risk to report a poorer health status[55] and to have an increased mortality risk.[19-22, 56] However, those studies were not designed with a specific focus on gender-related differences. *Chapter 6* assesses gender-related differences in 1-year health status scores and long-term adverse events in PAD patients.

Change in depressive symptoms following peripheral arterial disease diagnosis

Preliminary findings demonstrated a substantial burden of depression in patients with PAD (approximately present in 20%, range 16-36%),[27-29, 31, 35-38] specifically younger women with PAD seem to be vulnerable for depressive symptoms.[30] Recent findings also demonstrated that depression in PAD is associated with poorer patency rates, cardiovascular events and mortality.[31, 36, 37] Since it is generally assumed that depression status remains stable over time,[35, 39, 40] only few evaluated the course of depressive symptoms during follow-up.[35] Because depression is related to adverse outcomes,[31, 36, 37] it would be worthwhile to evaluate possible determinants for change in depressive symptoms over time, with the hopes that better understanding of the course of depression status may help to further evaluate patient-centered outcomes in the future.

8.2. New knowledge obtained from this thesis

8.2.1. Subpopulations in patients with peripheral arterial disease

Based on anatomical lesion location

Chapter 2 provides an extensive overview of patients' clinical characteristics, risk factors, psychological factors, and their symptom profile associated with their anatomical lesion location in a cohort of 701 patients with PAD. Two distinct patient profiles emerged based on anatomical lesion location. On the one hand, proximal lesions are most likely to be present in younger females who are less likely to be obese. On the other hand, distal lesions are more often seen in the elderly male patient without a partner and who is less burdened by symptoms of anxiety. Although 2 distinct PAD phenotypes were identified, no clear leg symptom profiles could be linked with these 2 groups. Patients tend to report a wide variety of symptoms, regardless of the anatomical lesion presentation, except for typical claudication symptoms, which seem to be more prevalent among patients presenting with distal lesions.

These observations may make physicians aware to not solely rely on patients' self-reported leg symptoms for guidance of diagnostic imaging, but to complement such information with a thorough history-taking and physical examination. Identification of subpopulations based on lesion characteristics might be useful for the application of preventative strategies. For example, younger patients might benefit from intensifying secondary prevention strategies while the older patient who is already burdened by cardiovascular comorbidity might benefit more from extensive tertiary prevention strategies. Whether initiatives to maximize prevention strategies in these groups will eventually lead to the reduction of patients' individual risk of adverse outcomes should be determined in future research.

Subpopulations based on pre-procedural health status

Since there is little information available about which PAD subpopulations may mostly benefit most from invasive vs. non-invasive treatment referral, *Chapter 5* identifies new subpopulations of patients with PAD according to their pre-procedural health status scores. It is demonstrated - in a cohort of 474 patients - that patients presenting with lower pre-procedural health status scores are more likely to be burdened by a

cardiovascular history, risk factors, and psychological comorbidities as compared with patients presenting with higher health status scores. In clinical practice, these findings may be meaningful for clinicians to identify patients who are vulnerable for a diminished health status and comorbid psychological factors. Medical factors, such as a cardiovascular history and other risk factors, might serve as indicators to identify those patients and – if necessary – to refer them for further psychological assistance.

Gender-related differences in peripheral arterial disease

Given the prior documented gender-related differences in health status and adverse outcomes,[19-22, 55, 56] and the recently launched 'call to action' from the American Heart Association[8] to focus on gender-related differences in PAD, *Chapter 6* evaluates gender-related differences in 1-year physical and mental health status in a cohort of 816 patients with PAD. Women were more likely to have a lower socioeconomic status (single status, lower education), to report symptoms of depression, and to have lower health status scores as compared with their male counterparts. In terms of cardiovascular history, comorbidity, and risk factors, men and women did not significantly differ from each other. These findings should make clinicians more aware that the psychological burden in patients with PAD is greater in women as compared with men. Whether identification of psychological comorbidities in women – followed by subsequent treatment - could possibly reduce womens' health status burden needs to be subject of future research.

Subpopulations in the psychological burden of peripheral arterial disease

PAD is not only associated with a diminished health status or quality of life,[8, 9, 14, 15, 17, 18, 24-27] but also with an increased risk of depression.[27-30] *Chapter 7* stratifies patients according to their baseline depressive symptoms in a cohort of 528 newly diagnosed PAD patients. Depressed patients are characterized by a lower educational status, diabetes, back pain, a shorter pain-free walking distance, and a Type D personality. Such characteristics in newly diagnosed patients with PAD should make clinicians aware of the fact that an underlying depression might be present in about a quarter of their PAD population. Timely referral of patients for psychological evaluation and coaching - in addition to their medical treatment - might help reduce the psychological burden of PAD that patients are facing.

8.2.2. New knowledge on the quality of the clinical decision-making process

Current guidelines recommend taking into account various factors to guide invasive treatment referral in patients with PAD.[8-10] However, prior observations suggest that significant variations in treatment practices are present.[44, 45, 57] We document what factors are actually being weighed in the clinical decision-making process and document site differences in invasive treatment referral in care among 2 vascular specialty clinics in the Netherlands. *Chapter 3* provides novel insights in this understudied aspect of PAD management. While patients' self-reported physical health status was only marginally taken into account in the choice for invasive treatment referral, the anatomical lesion location that patients presented with (i.e., proximal lesions) was indeed an important factor of consideration as recommended in current guidelines.

Although patients presented with similar characteristics, they were nearly twice as much likely to be referred for invasive treatment in one hospital as compared with the other. Possible explanations for the presence of practice variations in general might be found at the surgeon-level (volume, skills and use of endovascular procedures), site-level (hospital size, teaching status), or the intensity of provided care.[44, 58]

Our (preliminary) findings may open the discussion to better document practice variations in PAD health care and to evaluate the effect of variations in clinical practice on possible differences in (patient-centered) outcomes. Such information might be informative for clinicians, hospital administrators, insurers, and policy makers to reduce hospital variations in care and to prevent potential adverse outcomes. Evaluating the effect of practice variations on differences in outcomes might additionally serve as an effort to reach the most optimal treatment strategy for the individual patient.

8.2.3. Novel findings in peripheral arterial disease outcomes

Multiple adverse events

It is generally assumed that the extensiveness of generalized atherosclerosis is related to patients' prognosis: the more arterial beds are being affected simultaneously, the higher patients' risk of experiencing one or more adverse events.[48-50] However, both the extensiveness of arterial lesions or the risk for multiple serial adverse events over time have not been thoroughly studied for *lower-extremity* arterial lesions. *Chapter 4* touches upon this gap in knowledge by examining the association between extensiveness of *lower-extremity* lesions and patients' risk for having a first or multiple adverse events over time.

Chapter 4 has the potential to advance the field of PAD in multiple ways. It is demonstrated that about half of the population presented with multiple lower-extremity lesions. As hypothesized, having more extensive PAD is not only associated with an increased risk of experiencing a first event, but also with an increased risk of experiencing multiple serial events over time. These findings suggest that more extensive PAD might represent a phenotype that is associated with a more aggressive form of atherosclerosis, and it underlines the need to risk stratify patients quickly after their initial PAD diagnosis. Furthermore, clinicians may want to more closely monitor patients with more extensive PAD who might be facing increased risks of (multiple) adverse events over time. These monitoring strategies could, for example, consist of more aggressive risk factor management (e.g., optimizing lipid levels, blood pressure, smoking cessation counseling), optimizing pharmacotherapy (e.g., adjust dose of lipid lowering drugs, adherence to anticoagulants), adherence to supervised exercise therapy, as well as multidisciplinary consultation of other vascular medicine specialists. Such preventive efforts may help to prevent future adverse events.

In addition, imaging techniques – such as duplex ultrasound testing – can be used as a simple risk stratification tool to risk stratify patients according to the extensiveness of lower-extremity lesions that they present with upon their PAD diagnosis. Another benefit is that duplex ultrasound imaging is often easily accessible in vascular specialty clinics and has a favorable sensitivity and specificity for detecting significant lesions.[8, 9]

Despite these potential benefits of duplex ultrasound testing, it should first be evaluated whether imaging the whole lower-extremity arterial system or just a part of the arteries as guided by the clinical evaluation of patients' symptoms will be superior in risk-stratifying patients according to the extensiveness of their lesions. Furthermore, it should also be determined whether preventive strategies may indeed help to reduce the adverse event risk in high-risk patients as determined by the number of lower-extremity lesions. Last but not least, cost-effectiveness analyses will be necessary to evaluate whether duplex ultrasound testing is indeed a practical risk stratification tool for clinical settings.

Apart from the clinical insights that were derived from *Chapter 4*, we are also able to use a sophisticated methodology[59] that accounts for the complex reality of patients with PAD, i.e., having to deal with multiple cardiovascular events over time. By expanding traditional time-to-first event Cox regression models with a state-of-the art Cox-based intensity-elapsed time model, it was possible to incorporate information on multiple serial event risks and to demonstrate that myocardial infarction and mortality explained the increased risk of experiencing multiple events over time. Evaluating the risk of adverse events as a function of the extensiveness of patients' lower-extremity lesions might help to better risk stratify patients for experiencing multiple, serial, adverse events at their diagnosis of PAD. Future work is needed to explore whether care innovations for patients with more extensive PAD will eventually help to reduce their risk of having an adverse prognosis.

Health status benefits following invasive treatment

Chapter 5 provides novel insights in patients' 1-year change in self-reported health status benefits following invasive vs. non-invasive treatment referral as a function of pre-procedural health status – as opposed to documenting patency rates. It illustrates that greater health status benefits can be expected in patients having a lower pre-procedural health status and who are treated invasively. In addition, the number needed to treat to obtain clinically meaningful changes in 1-year health status was substantially lower in patients presenting with poorer pre-procedural health status scores.

Another important finding was that invasive treatment was frequently performed across the population, irrespective of patients' health status scores suggesting that invasive treatment might not always be offered to those who might need it the most. Because the primary treatment goal in PAD is improving patients' health status,[8-10] these findings can be useful for clinicians to help patients' understand what health status benefits can be expected after invasive vs. non-invasive treatment referral and to evaluate procedural-related risks and benefits of different treatment strategies. Such information might eventually help to improve the shared clinical-decision making process for invasive treatment referral between clinicians and their patients.

Gender-related differences in health status and outcomes

The presence of gender-related differences in health status was evaluated in *Chapter 6*. This study found that – in line with prior work – women had significantly worse health status scores as compared with men upon enrollment as well as 1-year following their PAD diagnosis. As a secondary aim, *Chapter 6* briefly touches upon gender-related differences in (all-cause) mortality and adverse events. Despite prior documented conflicting results in gender-related outcomes,[23, 60, 61] no absolute difference on adverse events between men and women was observed in the present study. These findings seem counterintuitive since clear evidence exists where women with coronary artery disease have a poorer prognosis as compared with men.[20, 62, 63] Future research should focus on designing prospective studies that explicitly evaluate gender-related differences in adverse events in patients with PAD (as proposed by the American Heart Associations' 'call to action').[8]

Change in depressive symptoms over time

Apart from health status, depression is another psychological burden that is evaluated in this thesis. *Chapter 7* is one of the first studies to explore determinants for change in depressive symptoms, and found – in accordance with prior studies[35, 39, 40] – that the presence of depressive symptoms remained rather stable over time. About 8% of patients improved in terms of depressive symptoms over the course of 1-year follow-up, whereas another 8% developed symptoms of depression. Although improvement in PAD-related symptoms was not the focus of *Chapter 7*, it might be hypothesized that clinicians should specifically be aware of underlying psychological factors in patients not reporting improvement in their symptoms or even deterioration when PAD-related measures (e.g., ABI, treadmill test) are promising. Creating awareness of possible underlying depressive symptoms and subsequent referral of patients for psychological coaching might help to improve patients' medical as well as their psychological burden of PAD.

8.3. Limitations and strengths of the present thesis

Before interpreting the results of the thesis, some potential limitations and strengths should be addressed.

8.3.1. Limitations

Several limitations were observed in the present thesis. First, all findings (*Chapters 2-7*) were based on observational research data. Ideally, when comparing different treatment strategies in PAD one would want to randomize patients to an invasive vs. non-invasive treatment arm, but randomization for treatment strategy was not possible (*Chapter 5*) due to the observational nature of the study. To overcome the possibility of selection bias, propensity-weight adjusted analyses were conducted for the propensity to undergo invasive vs. non-invasive treatment.

Second, although we greatly acknowledge the importance of using PAD-specific instruments, these measures were not always available when the cohort started to enroll the first patients in 2006 (e.g., Short Form 12 in *Chapters 3*, *5*, and *6*, and Hospital Anxiety and Depression Scale in *Chapter 7*).

Third, data were only collected from 2 vascular specialty clinics in the Netherlands. This may have limited our generalizability for detecting differences in real-world clinical practices in greater detail (*Chapter 3*). In addition, the data may only be generalizable to Dutch vascular specialty clinic settings since reimbursement rates for supervised exercise programs and access to such programs may differ across institutions and countries (*Chapters 3* and *5*). Although site variations were documented, it was not possible to detect nuanced differences in individual provider variability that could have explained the reason for the documented variations (*Chapters 3*).

Fourth, given the limited number of multiple events occurring during the study's follow-up, we might have been underpowered to evaluate effects in our multiple events sensitivity analyses. For power considerations, the risk of patients' adverse events was therefore assessed by the use of a composite endpoint (*Chapters 4* and *6*). The multiple events analysis in *Chapter 4* was additionally explored by a hierarchical approach to further grasp on what type of event would mostly explain patients' risk.

Finally, we explored what factors were weighed in the clinical-decision making process for invasive treatment referral in *Chapter 3*, and determined what health status benefits can be expected following invasive treatment referral in *Chapter 5*. Yet, we were unable to document patients' preferences for invasive treatment referral in addition to their self-reported health status (*Chapter 3* and *5*).

8.3.2. Strengths

In addition to the thesis' limitations, several strengths should be mentioned as well. First, we had a large homogeneous cohort available of newly diagnosed PAD patients that was enrolled prior to referral for any treatment strategy. For *Chapters 3* and *5-7* we were able to document pre-procedural characteristics that we could compare with follow-up measures.

Second, although only 2 vascular clinics were included in the study, it was possible to document on real-world clinical practices and diagnostic work-up procedures (*Chapters 2* and *3*). This made it possible to evaluate practice variations in the management of PAD (*Chapter 3*) and confirm preliminary evidence suggesting variations in care for PAD.[44-46, 57]

Third, because a wide variety of self-reported questionnaires on patients' leg symptoms, sociodemographics, and psychological aspects was available in addition to detailed information that was abstracted from patients' medical records (e.g., risk factors, medical history, vascular laboratory assessments, medication use, follow-up data on adverse events and mortality, and treatment practices), a rich dataset was available to address the various research questions of this thesis in great detail (*Chapters 2-7*).

Fourth, since complete and long-term follow-up data was available from medical record abstraction, *Chapters 4* and *6* are able to provide novel insights in patients' adverse events. *Chapter 4* additionally uses a novel state-of-the-art methodology[59] to assess patients' risk of experiencing multiple adverse events over time that can be considered as a true innovation because this has not yet been performed in PAD research.

Finally, the present dataset made it possible to address the identified gaps in the current knowledge of PAD through the various chapters (*Chapters 2-7*). These findings may set the stage for future research directions in the field of PAD.

8.4. Clinical implications and future research directions

8.4.1. Patient-centered vs. prognostic outcomes in subpopulations of PAD

Several new PAD subpopulations are identified in the separate chapters of this thesis. While identification of subpopulations may be clinically useful for health care providers so that they can better risk stratify patients for optimizing treatment and preventative strategies on a more tailor-made basis, the identification of PAD subpopulations alone may not be sufficient and additional information on differences in (patient-centered) outcomes in those subpopulations is needed. Furthermore, incorporating state-of-the-art modeling techniques for multiple events might help to more adequately assess patients' risk of multiple adverse outcomes over time and improving methodological aspects should be part of the research agenda as well. Only when such information will become available, we will be able to broaden the scope from identifying subpopulations in patients with PAD to integrating this knowledge that may help to move on towards initiatives that improve PAD health care for the individual patient.

Future multicenter registries studying patient-centered outcomes in real-world clinical practice are needed as a next step towards understanding and improving the clinical-decision making process. It is necessary for such studies to incorporate disease-specific health status instruments instead of generic tools. Evaluating patient-centered outcomes in a real-world clinical practice has the potential to document access to health care resources among different subpopulations. In an era where patient-centered outcomes are becoming increasingly important, future efforts should not only focus on the clinicians' perspective, but also evaluate patients' preferences in the shared clinical-decision making process for treatment referral. Informing patients on what (patient-centered) outcomes can be expected following their PAD diagnosis and weighing their treatment preferences might help to develop more tailor-made clinical-decision aids for the identified PAD subpopulations.

8.4.2. Improving the quality of the shared clinical-decision making process: An important role for vascular surgeons?

Most patients that will be evaluated for PAD in the Netherlands are being referred to vascular surgery specialty clinics.[64] Therefore, vascular surgeons could play an important role as health care provider to improve the quality of care and the shared clinical-decision making process in patients with PAD. Although PAD guidelines as well as patients' preferences are directive for treatment referral, the health care that is actually being provided to the individual patient is not systematically evaluated in routine clinical practice (e.g., "Does every patient receive antiplatelet drugs and statins?"). Development of more standardized protocols or health care checklists might be useful to document whether the care that is intended to be provided is indeed offered in each patient. This might additionally serve as a tool to concentrate the health care providers' attention to more vulnerable and high-risk subpopulations.

This thesis points out that some patients with PAD are more vulnerable as compared with others. For example, determining patients' health status upon PAD diagnosis might be useful to identify what patients may benefit most from various treatment strategies. Informing patients on health status benefits and risks to be expected for various treatment strategies allows patients to actively participate in the shared clinical-decision making process. Such initiatives might be an interesting thought, but may be difficult to implement and evaluate in daily clinical care. This should become part of the debate as to how to improve the quality of care for the individual patient. As main health care providers for PAD patients, vascular surgeons can play an important role helping to improve the quality of the shared decision making process.

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Chapter 9

Nederlandse samenvatting

9

NEDERLANDSE SAMENVATTING

Patiënten met perifeer vaatlijden hebben vernauwingen in de slagaderen van de benen. Deze vernauwingen (laesies) ontstaan door slagaderverkalking (atherosclerose) en leiden tot een verminderde bloedtoevoer. Hierdoor ervaren patiënten met symptomatisch perifeer vaatlijden pijnklachten, ongemak, of krampen in de benen die ontstaan tijdens het lopen, maar verdwijnen in rust (claudicatio intermittens). Patiënten met perifeer vaatlijden ervaren niet alleen een fysieke belemmering bij het lopen, maar hebben ook een lagere gezondheidstoestand en een verminderde kwaliteit van leven.

De primaire behandeling van perifeer vaatlijden is enerzijds gericht op de vermindering van pijnklachten en anderzijds op het verbeteren van de kwaliteit van leven. Doordat de risicofactoren om perifeer vaatlijden te ontwikkelen gelijk zijn aan die van andere hart- en vaatziekten, heeft een groot deel van de patiënten ook een vernauwing in de kransslagaderen (coronairen) of halsslagaderen (carotiden). Patiënten met perifeer vaatlijden hebben daarom een verhoogd risico op het doormaken van een cardiovasculair event (bijvoorbeeld een hartinfarct of beroerte) en overlijden.

Vergeleken met onderzoek dat is gedaan in patiënten met andere hart- en vaatziekten, blijft perifeer vaatlijden nog onderbelicht. Dit proefschrift richt zich daarom op 3 onderwerpen die nog onvoldoende onderzocht zijn in patiënten met perifeer vaatlijden. Allereerst richt het zich op het identificeren van verschillende subpopulaties op basis van anatomische lokalisatie van de vernauwing, presentatie van pijnklachten, zelfgerapporteerde gezondheidstoestand, geslachtsverschillen, en verandering in depressieve symptomen. Als tweede wordt het klinisch besluitvormingsproces voor de verwijzing voor invasieve behandeling in kaart gebracht. Verder worden patiëntgecentreerde uitkomsten (o.a. cardiovasculaire events, overlijden en verandering in gezondheidstoestand) gedocumenteerd voor de geïdentificeerde subpopulaties. Als laatste worden adviezen gegeven voor toekomstig onderzoek en klinische implicaties van de bevindingen in dit proefschrift.

Identificatie van subpopulaties

Op basis van anatomische lokalisatie van vernauwingen

Voorgaand onderzoek heeft aangetoond dat de verdeling van atherosclerose in de slagaderen in de benen varieert in anatomische lokalisatie en dat dit mogelijk gepaard gaat met een verschillend risicoprofiel. In *Hoofdstuk 2* worden duidelijk 2 verschillende patiëntenprofielen (subpopulaties) onderscheiden op basis van de anatomische lokalisatie van atherosclerose. Enerzijds wordt gezien dat patiënten met een vernauwing in de proximale vaten vaker vrouw zijn en minder vaak obees. Anderzijds zijn patiënten met een vernauwing in de distale vaten ouder, vaker man, vaker alleenstaand, en rapporteren zij minder vaak symptomen van angst. Hoewel patiënten een grote variëteit in symptomen rapporteren, worden er geen duidelijke verschillen gezien van deze symptomen op basis van anatomische lokalisatie. Echter, patiënten met distale vernauwingen zijn wel meer geneigd 'typische' klachten van claudicatio intermittens te rapporteren in vergelijking met patiënten met proximale vernauwingen.

Op basis van preprocedurele gezondheidstoestand

Hoewel richtlijnen beschrijven wanneer de clinicus over zou kunnen gaan tot invasieve behandeling bij patiënten met perifeer vaatlijden, bestaat er echter weinig informatie over welke specifieke patiëntengroepen de meeste baat hebben bij invasieve vs. niet invasieve behandeling als er gekeken wordt naar de te behalen gezondheidswinst. In *Hoofdstuk 5* komt naar voren dat patiënten met een lagere gezondheidstoestand vaker een cardiovasculaire voorgeschiedenis hebben, evenals andere risicofactoren en meer psychologische comorbiditeit vergeleken met patiënten met een betere gezondheidstoestand. Dergelijke informatie kan belangrijk zijn voor artsen om te identificeren welke patiënten zich initieel presenteren met een lagere gezondheidstoestand om zo een meer individueel behandelplan op te kunnen stellen.

Op basis van geslacht

Hoofdstuk 6 evalueert geslachtsgerelateerde verschillen voor fysieke en mentale gezondheidstoestand op 1-jaar na de diagnose van perifeer vaatlijden. Hieruit komt naar voren dat vrouwen vaker een lagere socio-economische status hebben, en vaker symptomen van depressie en een lagere gezondheidstoestand rapporteren vergeleken met mannen.

Deze bevindingen zouden clinici meer bewust moeten maken van de psychologische impact van perifeer vaatlijden en dat deze aanzienlijk groter is in vrouwen in vergelijking met mannen.

Op basis van psychologische symptomen

Naast het evalueren van de zelfgerapporteerde gezondheidstoestand van patiënten is er ook gekeken naar zelfgerapporteerde symptomen van depressie in *Hoofdstuk 7*. Een kwart van de patiënten gaf aan depressieve symptomen te hebben. Deze patiënten zijn vaker lager geschoold en hebben vaker diabetes, rugklachten, een kortere pijnvrije loopafstand, en een Type D persoonlijkheid in vergelijking met patiënten die geen depressieve klachten rapporteren. Dit grote aandeel van patiënten met depressieve symptomen zou de clinicus alert moeten maken op een onderliggende depressie die mogelijk van invloed is op het beloop van de behandeling en tijdige doorverwijzing.

De kwaliteit van het klinisch besluitvormingsproces

De huidige richtlijnen voor de behandeling van perifeer vaatlijden adviseren verschillende factoren mee te wegen alvorens over te gaan tot invasieve behandeling (dotterprocedure of operatie). *Hoofdstuk 3* toont aan dat verschillende factoren bijdragen aan de verwijzing voor invasieve behandeling. De zelfgerapporteerde gezondheidstoestand van patiënten wordt slechts marginaal meegewogen om al dan niet over te gaan tot invasieve behandeling. Echter, patiënten met een proximale vernauwing ondergaan ongeveer 4 maal vaker een ingreep in het eerste jaar na de diagnose.

Daarnaast werd gezien dat patiënten met gelijke risicoprofielen bijna 2 maal vaker een ingreep ondergaan in het ene ziekenhuis in vergelijking met het andere ziekenhuis. Mogelijke verklaringen hiervoor zouden gevonden kunnen worden op het niveau van de chirurg (aantal ingrepen, chirurgische ervaring en beschikbaarheid van endovasculaire procedures), op ziekenhuisniveau (capaciteit, opleidingsstatus), of de intensiteit van de geleverde zorg. Deze bevindingen zouden de discussie kunnen aanwakkeren om verschillen in behandelpraktijken en de daarmee gepaarde gaande effecten te documenteren. Evaluatie van mogelijke variaties in uitkomsten kunnen bijdragen aan het optimaliseren van de behandelstrategie voor de individuele patiënt.

Nieuwe bevindingen ten aanzien van patiëntgecentreerde uitkomsten

Cardiovasculaire uitkomsten

Patiënten met perifeer vaatlijden hebben een verhoogd risico op een cardiovasculair event (bijvoorbeeld een hartinfarct of beroerte) en overlijden. In *Hoofdstuk 4* is met nieuwe methodologische technieken gekeken naar het *aantal* vernauwingen in de onderste extremiteiten in relatie tot prognose (aantal events). Ongeveer de helft van alle patiënten met perifeer vaatlijden presenteert zich met multipele vernauwingen bij diagnose. Patiënten met multipele vernauwingen hebben niet alleen een verhoogd risico op het doormaken van één event, maar ook op meerdere events. Hierbij wordt gedacht dat patiënten met multipele vernauwingen mogelijk een meer agressieve vorm van atherosclerose hebben. Deze resultaten geven aan dat het belangrijk zou kunnen zijn om patiënten al ten tijde van diagnose in te delen in subgroepen aan de hand van het aantal vernauwingen. Of een meer agressieve behandeling dan ook zal leiden tot een betere prognose zal toekomstig onderzoek uit moeten wijzen.

Gezondheidstoestand na invasieve behandeling

Hoofdstuk 5 evalueert de verandering in gezondheidstoestand na verwijzing voor invasieve vs. niet invasieve behandeling voor perifeer vaatlijden. Hieruit komt naar voren dat patiënten met een lagere gezondheidstoestand ten tijde van diagnose de grootste vooruitgang in gezondheidstoestand boeken na invasieve behandeling. Het aantal te behandelen patiënten om een significante verbetering van gezondheidstoestand te bereiken (numbers needed to treat) was substantieel lager bij patiënten met een lagere gezondheidstoestand bij diagnose vergeleken met patiënten met een betere gezondheidstoestand. Deze informatie is klinisch relevant, omdat clinici patiënten beter kunnen informeren over de te verwachten gezondheidswinst na invasieve vs. niet invasieve behandeling in aanvulling op de risico's die gepaard gaan met de verschillende behandelopties.

Geslachtsverschillen in gezondheidstoestand en prognose

Met het oog op patiëntgecentreerde uitkomsten laat *Hoofdstuk 6* ook zien dat de gezondheidstoestand van vrouwen niet alleen lager is ten tijde van diagnose in vergelijking met mannen, maar dat dit ook het geval is op één jaar na het stellen van de diagnose. Qua prognose (cardiovascular event en overlijden) werd er geen verschil tussen mannen en vrouwen gevonden in de huidige studie. Gezien de tegenstrijdige resultaten uit voorgaande studies zullen toekomstige studies geslachtsverschillen duidelijker in kaart moeten brengen.

Verandering van depressieve symptomen over de tijd

Hoofdstuk 7 heeft niet alleen gekeken naar depressieve symptomen ten tijde van diagnose, maar ook naar factoren die mogelijk van invloed zijn op de verandering van depressieve klachten over de tijd. Overeenkomstig met enkele voorgaande studies laat *Hoofdstuk 7* zien dat de aanwezigheid van depressieve symptomen stabiel is over tijd. Slechts 16% geeft aan verbetering of verslechtering van symptomen te bemerken op één jaar na de diagnose van perifeer vaatlijden. Deze bevindingen suggereren het belang van het herkennen van depressieve klachten door de clinicus, omdat aanwezigheid van depressieve symptomen een behandeling voor perifeer vaatlijden – gericht op verbetering van klachten en kwaliteit van leven – in de weg kan staan.

Conclusie

De resultaten in dit proefschrift tonen aan dat patiënten met perifeer vaatlijden een kwetsbare patiëntengroep omvat met een verhoogd risico op comorbiditeit, een slechte prognose, een verminderde gezondheidstoestand en aanwezigheid van depressieve symptomen. Binnen de groep van patiënten met perifeer vaatlijden kunnen verschillende subpopulaties geïdentificeerd worden met elk hun eigen kenmerken en kwetsbaarheden. Daarom is het essentieel om de behandeling conform de richtlijnen op te volgen, maar deze af te stemmen op de kenmerken en wensen van de individuele patiënt. Een dergelijke benadering kan bijdragen aan het verbeteren van de kwaliteit van het gezamenlijke klinische besluitvormingsproces waar zowel arts als patiënt een belangrijk deel van uitmaken.

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ABOUT THE AUTHOR

CURRICULUM VITAE (ENGLISH)

Moniek van Zitteren was born on December 12, 1985 in Roosendaal and Nispen, the Netherlands. She completed her pre-university education at the R.K. Gymnasium Juvenaat H. Hart, Bergen op Zoom, in 2004, and immediately started her medical training at the Erasmus University Medical Center in Rotterdam. In December 2005, she was selected to participate in the NIHES (Netherlands Institute for Health Sciences) Master of Science Program in Clinical Epidemiology, which she completed in August 2009 with a subspecialty in Genetic Epidemiology. Simultaneously, she continued her clinical rotations at the St. Elisabeth Hospital in Tilburg. During her clinical rotations, she worked together with the vascular surgeons of the St. Elisabeth Hospital on several research projects.

In February 2011, she obtained her medical degree (cum laude) and subsequently started a 2-year PhD-track at Tilburg University focusing on patient profiles and outcomes in patients with lower-extremity peripheral arterial disease. Directly after completing her PhD-track, she continued her medical career as a resident (ANIOS) at the department of Surgery at the St. Elisabeth Hospital in Tilburg.

OVER DE AUTEUR

CURRICULUM VITAE (NEDERLANDS)

Moniek van Zitteren werd geboren op 12 december 1985 te Roosendaal en Nispen, Nederland. Na het behalen van het eindexamen aan het R.K. Gymnasium Juvenaat H. Hart te Bergen op Zoom in 2004, startte ze meteen met de opleiding Geneeskunde aan het Erasmus Medisch Centrum te Rotterdam. Daarnaast werd ze in 2005 toegelaten tot het NIHES (Netherlands Institute for Health Sciences) Master of Science programma in Klinische Epidemiologie, die ze met een subspecialisatie in Genetische Epidemiologie afrondde in augustus 2009. Gelijktijdig startte ze met haar co-schappen in het St. Elisabeth Ziekenhuis te Tilburg. Tijdens haar co-schappen werkte ze samen met de vaatchirurgen in het St. Elisabeth Ziekenhuis aan verschillende onderzoeksprojecten.

In februari 2011 behaalde ze haar Artsexamen (cum laude) en begon direct daarna aan een 2-jarig promotietraject aan de Universiteit van Tilburg dat zich richtte op profilering en uitkomsten/prognose bij patiënten met perifeer arterieel vaatlijden van de onderste extremiteiten. Direct na afronding van haar proefschrift zette ze haar medische carrière voort als arts-assistent (niet in opleiding) op de afdeling Chirurgie van het St. Elisabeth Ziekenhuis te Tilburg.

APPENDIX – SAMENSTELLING COMMISSIE

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