MANAGEMENT OF PATIENTS WITH INTERMITTENT CLAUDICATION

SANDRA SPRONK

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CONTENTS

1 GENERAL INTRODUCTION

GENERAL INTRODUCTION

Intermittent claudication is the first and mildest manifestation of peripheral arterial disease, caused by the atherosclerotic process of progressive narrowing of one or more of the arteries of the peripheral circulation.[1] If the arterial system fails, it results in a progressive oxygen debt, experienced by the patient as cramping muscle pain during walking or other physical activity, which forces the patient to pause. The incidence of intermittent claudication increases with age, especially among men, with an annual incidence rate of 0.7%, 3.9%, and 10.6% among 35-44 year, 45-54 year, and 55-64 year old men respectively.[2] In women, the incidence rates are approximately 50% lower than in men.[2] The development of intermittent claudication is accelerated by the same cardiovascular risk factors as known for other expressions of atherosclerotic disease (i.e. coronary heart disease and cerebro-vascular disease). These risk factors are smoking, diabetes mellitus, hypertension, and hyperlipidaemia.[3,4]

To localize the narrowed or occluded artery, non-invasive or invasive imaging tests are needed. Traditionally, digital subtraction angiography has been considered as the "gold standard" and images are easily displayed and interpreted for planning treatment, however it is invasive and associated with a risk of morbidity and mortality.[5] Therefore, non-invasive imaging modalities are increasingly prefered for the evaluation of patients with intermittent claudication. duplex ultrasound was introduced into clinical practice in the early 80's and can be used for preintervention decision making.[6] Problems may arise, however, when evaluating the aortoiliac arteries that cannot be visualized in their entirety in the 5%-25% of patients who are extremely obese, have abundant intestinal gas, or who have particularly tortuous or calcified iliac arteries.[7,8]

It would be attractive, if one could rapidly evaluate the aortoiliac arteries for the presence of significant obstructive disease without having to visualize these arteries along their entire length. This would reduce the number of indeterminate results of duplex ultrasound, reduce the examination time for a complete Duplex Ultrasound examination and might also reduce the existing moderate observer variability in evaluating the aortoiliac segment.[9] Potentially, such rapid evaluation of the aortoiliac arteries might be provided by assessing the duplex waveform as measured distally at the level of the common femoral arteries.[10-13] It is known that the waveform distal to a significant obstruction often changes in character, for example from a normal triphasic waveform proximal to a stenosis to a monophasic waveform distal to the stenosis. There are, however, only few data in the literature that have addressed the question how accurate a marker a duplex ultrasound waveform of the femoral artery is in showing or excluding significant aortoiliac obstruction.

Intermittent claudication is neither a life-threatening nor limb-threatening form of peripheral arterial disease. Nonetheless, for those so afflicted, intermittent claudication has a negative impact on health-related quality of life and has been associated with increased, risk of mainly cardiovascular disease.[14] Improvement in health-related quality of life is the ultimate goal of treatment of intermittent claudication. The general consensus to reach that goal is that all patients presenting with intermittent claudication should initially be treated with exercise training and only if symptoms fail to improve are invasive procedures considered.[3, 15, 16] Despite this general consensus, however, percutaneous transluminal angioplasty is increasingly performed as the first treatment. Exercise training has been recommended since Larsen and Lassen reported their results in 1966.[17] Exercise training is a non-invasive treatment for patients with intermittent claudication and has shown to improve patients' walking distance. However, level of evidence A applies only to supervised exercise programs and not to unsupervised programs (level of evidence B).[18] Meta-analyses and systematic reviews showed significant improvements in physical functioning with an increase of the walking distance of about 180%.[19,20] However, in the literature the type of exercise training varies from home-based to hospital-based programs and the definition of supervised exercise training and non-supervised exercise training also varies widely, especially in Europe.[21-23] The standard exercise training in Western European countries is home-based, mostly for logistical reasons, whereas in the United States most guidelines recommend supervised treadmill exercise training.[24] Not only the type of exercise training varies, but also the follow-up differs across studies.[20, 21, 23]

The percutaneous revascularization techniques in peripheral arterial disease were initiated by Dotter and Judkins in the early 60's.[25] The relatively low mortality and morbidity risk made percutaneous transluminal angioplasty an established treatment option for patients with intermittent claudication. It has 5 year patency rates of 80% for aortoiliac and 60% for femoropopliteal disease.[26-29] However, not all arterial lesions are suitable for percutaneous transluminal angioplasty. The current view is that percutaneous transluminal angioplasty should be performed in patients with short focal lesions. The precise criteria, however, are still a matter of debate.[3]

There still is no convincing evidence that an angioplasty procedure provides significant functional benefit and improvement in health-related quality of life compared to conservative exercise training after long-term follow-up. It is common knowledge that atherosclerotic disease is a generalized process and presents as a multi-level disease. Percutaneous transluminal angioplasty is a local form of treatment, and it is therefore not surprising that following percutaneous transluminal angioplasty patients may relapse with ipsilateral or contralateral symptoms representing progressive disease at other sites. The benefit of percutaneous transluminal angioplasty may have a short-term effect only.

In addition to health-related quality of life, however, one needs to consider costs and cost-effectiveness. It is likely that initial hospital costs of endovascular revascularization are higher than those of exercise training. Besides these initial hospital costs, costs of follow-up are important to take into account, such as the costs of diagnostic tests for recurrent symptoms and secondary treatment. Many physicians consider exercise training an inexpensive and effective treatment to improve a patient's absolute claudication distance[15,19,30], whereas, from the societal perspective it may not be as inexpensive as it seems, due to the required time investment on the part of the patient. This is accompanied by an ongoing debate about the optimal treatment for patients with intermittent claudication, in which costs play an important role.[31,32]

Furthermore, because risk factors for intermittent claudication do not differ from those of atherosclerotic disease, many patients have both intermittent claudication and coronary artery disease.[33] Coronary artery disease is the main cause of death in the United States.[1] Millions of Americans have a history of myocardial infarction or experience angina pectoris.[1] Approximately one third of men and one fourth of women with known coronary artery disease also have peripheral arterial disease.[34] Many coronary artery disease patients (on average 300,000 per year) enter a rehabilitation program in the United States with the objective of reducing cardiac symptoms, improving physical functioning, improving cardiovascular risk factors, reducing mortality, reducing myocardial infarctions, and improving psychological well-being.[35,36] Patients with coronary artery disease who have peripheral arterial disease, however, are hampered in their cardiac rehabilitation program because they either discontinue the program prematurely or are unable to achieve their target heart rate due to their

limited walking distance. As a result these patients have an increased risk of cardiac events during follow-up (20%-60% increased risk for MI).[37,38]

How clinical effectiveness of a cardiac rehabilitation program is influenced by peripheral arterial disease, however, is still unknown. Therefore, management that focuses on improving of target heart rate as well as improving walking distance may be better in patients with both intermittent claudication and coronary artery disease. New rehabilitation strategies which include the diagnosis and treatment of intermittent claudication in patients with coronary artery disease undergoing cardiac rehabilitation may improve the results of current cardiac rehabilitation.

AIM AND OUTLINE OF THIS THESIS

The primary purpose of this thesis was to compare the clinical effectiveness and cost-effectiveness of endovascular revascularization to supervised hospital-based exercise in patients with intermittent claudication.

Though intermittent claudication is not a limb-threatening or a life-threatening disease, the loss of walking ability and the experience of pain with ambulation seem to result in a deterioration of physical and emotional well-being. The impact of intermittent claudication and its treatment on health-related quality of life are presented in **Chapter 2**.

In **Chapter 3**, a systematic review of the existing literature on exercise training versus percutaneous transluminal angioplasty in patients with intermittent claudication is presented. Variables across the studies were not uniformly defined or measured under identical conditions. Therefore, we performed a meta-analysis using a random effects model.

A randomized controlled trial was performed to evaluate the clinical effectiveness and cost-effectiveness of endovascular revascularization compared to supervised hospital-based exercise in the treatment of patients with intermittent claudication. **Chapter 4** presents the clinical effectiveness after endovascular revascularization versus supervised hospital-based exercise of this randomized controlled trial and **Chapter 5** presents the associated cost-effectiveness analysis.

How the clinical effectiveness of a cardiac rehabilitation program is influenced by peripheral arterial disease is described in **Chapter 6**. This chapter explores whether the clinical effectiveness of cardiac rehabilitation was related to the presence of peripheral arterial disease.

New management strategies for coronary artery patients undergoing cardiac rehabilitation are evaluated in **Chapter 7**. These strategies include the diagnosis and treatment of peripheral arterial disease and a comprehensive vascular rehabilitation program. The effectiveness, costs and relative cost-effectiveness of these new rehabilitation strategies are evaluated in an analytic Markov decision model.

In **Chapter 8** a diagnostic test evaluation is described. Duplex ultrasound is often used to plan the treatment strategy for patients with peripheral arterial disease. However, duplex ultrasound is operator-dependent and does not provide a "roadmap" of the arterial system. The accuracy, predictive value and observer agreement of the Duplex Ultrasound waveform at the common femoral artery as a marker of significant aortoiliac disease is assessed.

Finally, **Chapter 9** integrates the main findings of the previous chapters and relates them to current clinical practice. This chapter contains a general discussion of treatment for intermittent claudication and of management strategies for peripheral arterial disease in patients with coronary artery disease. Relevant methodological issues are discussed and suggestions are made for clinical practice and future research.

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2 IMPACT OF CLAUDICATION AND ITS TREATMENT ON QUALITY OF LIFE

IMPACT OF CLAUDICATION AND ITS TREATMENT ON QUALITY OF LIFE

Improvement in quality of life is the ultimate goal of healthcare for the treatment of intermittent claudication. Until recently, the measures of success after therapy were those derived from the vascular laboratory, including ankle-brachial indices and ankle and toe pressures. There are now several validated and reliable survey instruments that can assess patient-reported quality of life in a generic or disease-specific manner. Major survey instruments are reviewed. The information gathered through these quality-of-life assessment tools is important to all those involved in the care of patients with peripheral arterial disease. Although claudication is neither life- nor limb-threatening, it has a significant negative impact on quality of life, as measured by these instruments. Patients so afflicted report more bodily pain, worse physical functioning, and worse perceived health, in addition to limited walking ability. These measures of quality of life do not correlate with standard parameters of ankle-brachial index or ankle pressures. Treatment of the claudicant with exercise therapy and percutaneous or open revascularization also impacts quality of life. Each of these modalities is capable of improving quality of life, but some are associated with decline over time. The major benefits and risks to quality of life of these specific forms of treatment for the claudicant are reviewed. This data demonstrates that patients suffering from symptoms of intermittent claudication are best served by therapies that address their major self-reported impediments to quality of life.

The primary goal of healthcare is improvement in quality of life. This is certainly true of patients with peripheral arterial disease. Intermittent claudication (IC) is neither a life-threatening nor limb-threatening form of lower extremity ischemia. Nonetheless, for those so afflicted, claudication has a negative impact on quality of life. Until now, most vascular specialists would agree. The extent to which this form of peripheral artererial disease (PAD) disrupts a patient's life remains somewhat controversial. This is due to the fact that physical examination information and clinical data, such as ankle-brachial index (ABI), do not adequately describe the impact of claudication on quality of life. This was well-demonstrated by Pell,[1] who interviewed 201 patients with new-onset claudication and asked them to rate their quality of life prior to their visit with a vascular specialist. The investigator then obtained the vascular specialist's opinion regarding the impact of claudication upon the patient's quality of life, based upon medical history and physical examination. They found that the correlation between physician and patient assessment was poor. Because the impact of the disease upon the patient's life and level of functioning may be quite variable, even for similar clinical levels of ischemia, surgeons frequently overestimated the effect of claudication.[1] There is little correlation between clinical parameters of vascular disease, such as ABI, and the patient's self-reported level of disability. In a study of 555 patients, Feinglass and colleagues[2] recorded the ABI and the patient's self-reported level of physical functioning and walking ability. There was only a modest correlation between these measures. Patients with only a slight reduction of ABI to a level of 0.8 to 0.9 indicated that they had significant impairment of walking ability, whereas some patients with an ABI reduced to a near limb-threatening level of 0.4 to 0.5 reported that they were able to maintain high levels of physical functioning and walking ability. Similarly, an assessment of 157 patients with treadmill walking distance, ABI, and a quality-of-life survey documented poor correlation between the clinical parameters of walking ability and ABI and the measured quality of life.[3] These findings indicate that clinical measures, such as ABI, vessel and graft patency, and limb salvage, effectively assess the physiologic impact of claudication and its treatment, but do not adequately describe the overall patient status or the benefit or adverse effect of treatment on quality of life. To accomplish this, specific tools designed to elicit the effects of disease and treatment have been used.

QUALITY-OF-LIFE ASSESSMENT

Because IC is not a life-threatening condition, but limits patients' well-being, quality of life is considered the most important outcome.[4] Quality-of-life measures can be divided into generic (Table 1) and disease-specific measures. Subsequently, disease-specific measures can be divided in clinical assessment for identification of a disease (such as the Walking Impairment Questionnaire (WIQ)) versus descriptive healthstatus measures (Table 2). Generic measures can be divided in health descriptive versus valuation/preference-based measures.

The most common generic descriptive health measures used in evaluating quality of life in patients with PAD is the Medical Outcomes Study Short-Form 36 (SF-36).[5,6] The SF-36 was developed to evaluate physical, social, and physical role functioning of patients and to elicit their perceptions of their general health and well-being in eight different health dimensions (Table 3).[6] Previous studies demonstrated that the dimensions of physical functioning, role-functioning limitations due to physical problems, bodily pain, and general health are the most relevant dimensions to describe the health status of PAD. The scoring per dimension is valued on a 100-point scale from 0 (worst outcome) to 100 (best outcome). The reported mean value for patients with IC is 42 (±13) for physical functioning, 40 (±34) for physical role functioning, 47 (±11) for bodily pain, and 61 (±14) for general health.[7]

Table 1: Generic Quality-of-Life Instruments*

Nottingham Health Profile
EuroQol Health Assessement
Sickness Impact Profile
Medical Outcomes Study SF-36
Quality of Well-Being Scale

*The most commonly used generic quality-of-life instruments used to assess all comorbid conditions that can accompany vascular disease.

Another generic descriptive health measure was developed by the The World Health Organization (WHOQOL). The WHOQOL produces a profile of scores across six broad domains of quality of life and some 24 facets of quality of life. The six domains are: physical domain, psychological domain, level of independence, social relationships, environment, and spirituality/ religion/personal beliefs. Within each domain, several subdomains (facets) of quality of life summarize that particular dofacets "pain and discomfort" and "energy and fatigue." The scoring on each facet and domain can range from 4 to 20, in which higher scores indicate better functioning on the respective domain of quality of life, except for the facets pain and discomfort, negative feelings and dependence on medication and treatments, which have an inverse score. The reported mean value for the overall quality of life in patients with IC is 14.5 (±2.8).[8]

Table 2: Quality-of-Life Instruments and Impact of Intermittent Claudication

Instrument	Questionnaire	Scoring	Mean (+/-SD)	Reference
Disease-specific/ identification of intermittent claudication	Walking Impairment Questionnaire:	0-100		
	Distance*		26 (3)	14
	Speed*		33 (15)	14
	Stair climbing*		47 (9)	14
Disease-specific descriptive health measure	Vascular Quality of Life Questionnaire	0-7	3.7 (1.2)	10
	Claudication Scale Questionnaire	0-100		
	Daily life		62 (25)	11
	Pain		59 (21)	11
	Social life		89 (17)	11
	Specific fears		78 (22)	11
	Mood		81 (19)	11
Generic descriptive health measure	Short-Form 36 (SF-36)	0-100		
	Physical functioning†		42 (13)	7
	Physical role functioning†		40 (34)	7
	Bodily pain†		47 (11)	7
	General health†		61 (14)	7
	World Health Organization	4-20		
	Overall quality of life		14.5 (2.8)	8
	Physical		13.4 (2.4)	8
	Psychological		14.2 (2.4)	8
	Level of independence		13.1 (2.6)	8
	Social relationships		15.2 (2.7)	8
	Environment		16.1 (2.9)	8

* Scores are the weighted mean from the claudicants with ABI ≤ 0.6 and claudicants with ABI > 0.6.
† Scores are the weighted mean from the exercise group of the systematic review.

Table 3: Medical Outcomes Study 36-Item Health Survey (SF-36)

Areas of Assessment
Perception of health
Psychological well-being
Role limitations due to physical health problems
Role limitations due to mental health problems
Physical function
Social relations
Pain
Fatigue

Disease-specific descriptive health measures available for IC are the Vascular Quality of Life Questionnaire, and the Claudication Scale questionnaire. The Vascular Quality of Life Questionnaire is a questionnaire especially developed for patients with PAD and is responsive to measure subtle effects after, for example, exercise training or percutaneous transluminal angioplasty (PTA).[9] The questionnaire contains five domains (activity, symptom, pain, emotion, and social functioning), in which 0 means death and 7 indicates maximum health. The average value over these domains that has been reported for patients with IC is 3.7 (±1.2) (Table 2).[10] A disease-specific descriptive health measure, which is specially developed for patients with IC, is the Claudication Scale Questionnaire.[11] It originally consisted of 80 items in nine dimensions, but the long form made it unsuitable for use in clinical trials, so a short form was developed with the following dimensions: daily life (9 items), pain (10 items), social life (4 items), specific fears (13 items), and mood (11 items). Scores varied from 0 (worst outcome) to 100 (best outcome) and the mean reported value for patients with IC for these domains are 62 (±25) for daily life, 59 (±21) for pain, 89 (±17) for social life, 78 (±22) for specific fears, and 81 (±19) for mood.[11]

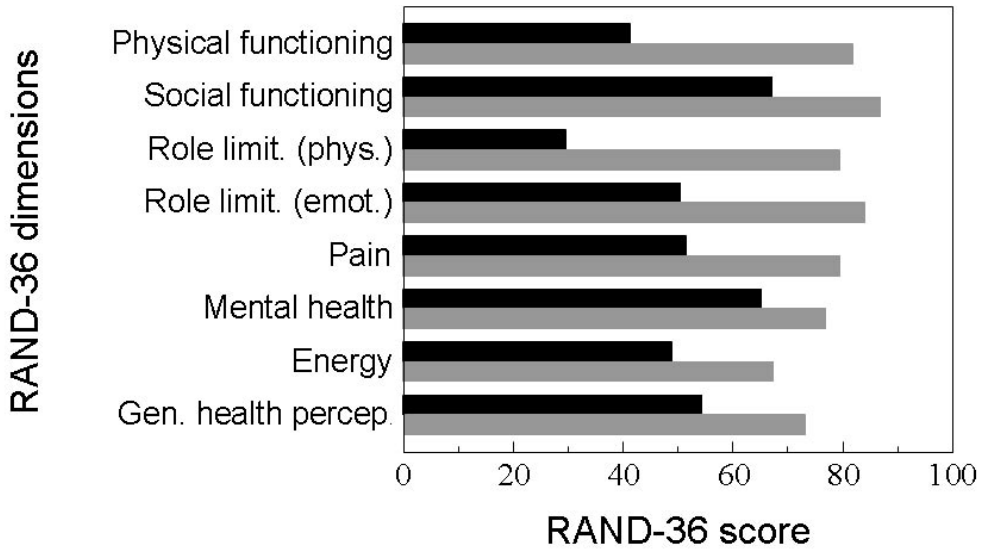
Disease-specific questionnaires can provide patient-reported information regarding the limitations imposed by claudication. The severity of IC as experienced by a patient can be assessed with the use of questionnaires like the WIQ.[12] This questionnaire has been used to evaluate walking ability in patients with IC before and after treatment.[13] The WIQ has three domains: walking distance, walking speed, and stair climbing, which together characterize the degree of walking impairment in patients with PAD.[13,14] For each domain symptom, scores range from 0% (worse outcome) to 100% (best outcome). Distance summary scores range from 0% (patients unable to walk 20 feet without stopping to rest) to 100% (patients able to walk five blocks without stopping to rest). The weighted mean value that has been reported for patients with IC was 26 (±3). Summary scores for walking speed range from 0% (patients unable to walk one block slowly without stopping to rest) to 100% (patients able to jog one block without stopping to rest). The weighted mean value that has been reported for patients with IC was 33% (±15). Stair-climbing scores ranged from 0% (patients unable to climb one flight of stairs without stopping to rest) to 100% (patients able to climb three flights of stairs without stopping to rest). The weighted mean value that has been reported for patients with IC was 47% (±9).[14]

Utilizing these patient-assessment tools, the impact of claudication and its treatment on patient quality of life has been assessed.

IMPACT OF CLAUDICATION ON QUALITY OF LIFE

Although IC is not limb-threatening, the loss of walking ability and the experience of pain with ambulation seem to result in a deterioration of physical and emotional well-being. In a study of claudicants using the Rand-36 generic quality-of-life instrument, Bosch and Hunink[15] were able to document that patients had significantly lower scores in all eight domains, especially physical function and role limitations due to emotional impact, compared to a control population without claudication (Fig 1). This finding was confirmed in a broader epidemiologic assessment in Scotland. A community-based study utilizing ABI, SF-36, and the Rose Intermittent Claudication Questionnaire, confirmed the negative impact of claudication on quality of life. Evaluating 53 patients with documented IC and comparing them to 327 patients without symptoms of PAD, Dumville and colleagues[16] also noted reductions in physical functioning, role limitations due to physical dysfunction, role limitations due to emotional dysfunction, bodily pain, energy, and general health perception. Only social functioning and mental health were spared the negative impact of claudication.

Figure 1: General health status in patients with claudication (dark bars) and without claudication (light bars) as measured by the Rand-36.



Reproduced from Bosch JL, Hunink MG. The relationship between descriptive and valuational quality-of-life measures in patients with intermittent claudication. Med Decis Making 1996;16:217-225.

This generalized adverse effect of claudication appears to be related more to walking distance than measured clinical parameters. The imposed limitations of ambulation have both physical and emotional effects. The impact of walking distance and quality of life was documented in a study of 80 patients with Fontaine Stage II PAD. These patients were evaluated with the WIQ and the SF-36, in addition to ABI and a 6-minute walking test. The results of the 6-minute walking test correlated well with quality-of-life scores. Patients with more limited walking abilities had worse scores on the physical function and role limitations due to the physical dysfunction subscales of the SF-36.[17] Any additional limitation in walking ability, whether by worsening atherosclerosis or by comorbid conditions, serves to worsen the patient's perception of quality of life. This was recently demonstrated by Gardner and colleagues,[18] who examined the walking ability and quality of life of claudicants with and without metabolic syndrome. This syndrome is marked by abdominal obesity, hypertriglyceridemia, low high-density lipoprotein, hypertension with a systolic pressure 130 mm Hg and a diastolic pressure 85 mm Hg, and a fasting glucose 110 mg/dL.[18] These investigators noted that patients with IC and metabolic syndrome have a walking distance 29% shorter than claudicants without manifestations of the syndrome. This reduction in walking ability in the setting of additional comorbidities was reflected in lower quality-of-life scores documented by the SF-36, with the most prominent impact upon general health, vitality, and bodily pain scores. Similar findings were noted by Breek and associates,[19] who evaluated 200 consecutive claudicants with the WHOQOL and attempted to stratify results according to the Society of Vascular Surgery/International Society of Cardiovascular Surgery classification for claudication. They noted that reduced walking distance correlated with physical scores on quality-of-life assessment, such as level of independence, working capacity, and mobility. Increasing comorbidities correlated with lower overall quality-of-life scores.[19] The emotional effects of IC have also been directly assessed with stress-specific measurement tools, as was done by Aquarius and colleagues.[20] Using the Perceived Stress Scale and the Rand-36, these investigators evaluated the impact of calf pain on 188 patients with new-onset claudication, documented by symptoms; physical examination; ABI; and treadmill walking test. Perceived stress was inversely proportional to walking distance, with a shorter walking distance correlating with greater perceived stress. Greater perceived stress, and not level of reduction in ABI, was associated with a poorer quality of life.

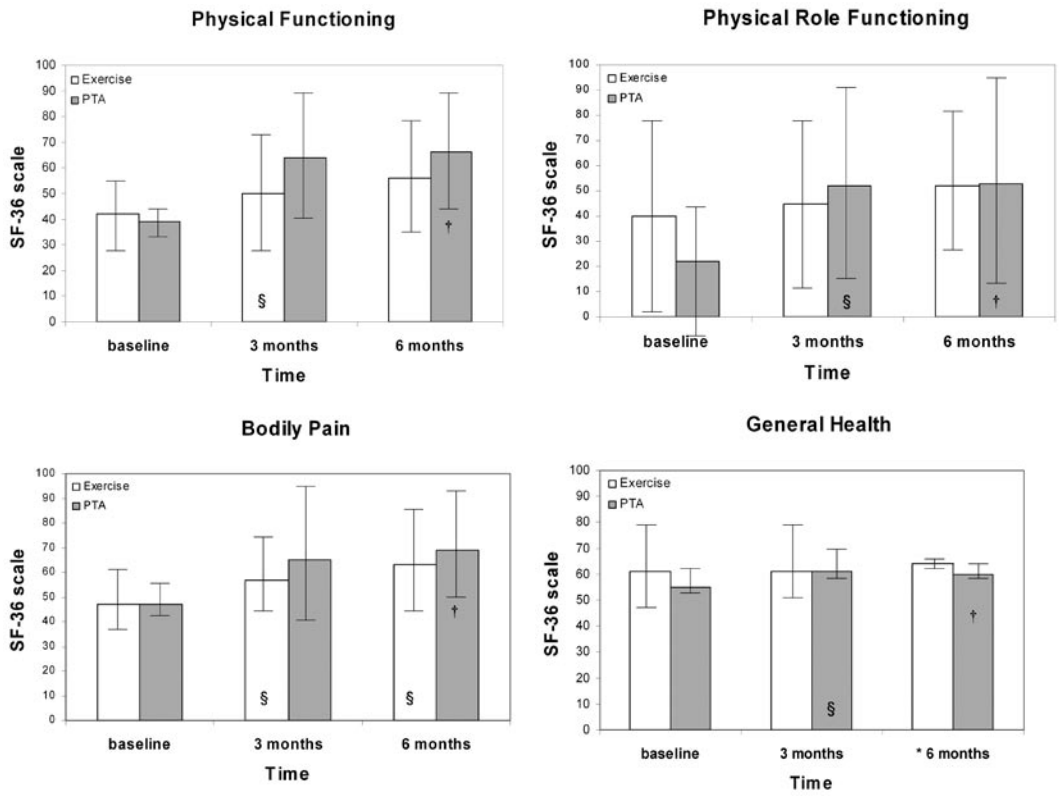
Although the most common disability associated with claudication, there are other studies that suggest that laboratory measurement of walking distance may not specifically correlate with quality of life. For example, Barletta and colleagues[21] evaluated treadmill performance and perceived quality of life with the McMaster Health Index Questionnaire, a validated generic tool, in 251 claudicants and 89 age-matched controls. They noted poorer scores in physical, emotional, and social function in claudicants compared with controls. The reductions, however, did not correlate with treadmill walking distance.[21] Thus, laboratory measurement of walking distance may not replicate the limitations experienced by the patient outside of the vascular laboratory. Nonetheless, these studies and numerous others that have evaluated the impact of intermittent claudication on patients, have documented a significant adverse impact upon quality of life.

IMPACT OF TREATMENT OF IC ON QUALITY OF LIFE

Treatment options for IC range from walking exercise programs to pharmacological treatment to PTA, with or without stent placement, to bypass surgery. The general consensus is that all patients presenting with IC should initially be treated with walking exercise and only if symptoms fail to improve, should invasive procedures be considered.[4,22,23] Despite this general consensus, however, PTA and other invasive forms of treatment are occasionally used as first-line therapy. Regardless of the approach to therapy, each of these modalities has associated benefits and adverse effects that may, ultimately, affect quality of life. Establishing the impact of treatment on quality of life has been difficult because of the limited number of studies with complete information.

Control of risk factors for atherosclerosis and participation in an exercise program has been shown to be sufficient to improve quality-of-life scores in claudicants. Imfeld and associates[24] compared the impact of supervised exercise therapy, supervised exercise therapy with cilostazol, and unsupervised

Figure 2. Weighted means and 95% confidence interval of SF-36 dimensions of physical functioning, physical role functioning, bodily pain, and general health for the exercise training and PTA group at baseline and at follow-up.



* Significant difference between the two groups.

† If 6 months values were not available, the 12 months values were used.

§ Significant improvement in group during follow-up.

exercise in a group of claudicants. SF-36 quality-of-life surveys were obtained before and 3 months after treatment. They noted that all patients had improved quality-of-life scores, but the scores did not correlate with increases in walking distance.[24] This suggests that even nominal increases in walking distance can be associated with greater improvements in quality of life. While there are clearly inconveniences associated with exercise programs, including delayed onset of increased walking ability, the time required, and some cost, there is little risk and few adverse effects from these programs.

In a broader assessment of the impact of exercise therapy on quality of life, Spronk and associates[7] systematically reviewed the published data on the short- and long-term effects on both functional capacity and quality of life of exercise training and PTA in patients with claudication.

All articles between 1980 and February 2003 were included if patients with IC were treated with exercise training or PTA, and both functional capacity and the SF-36 quality-of-life scores were reported of at least 3 months follow-up. Data were pooled using the random-effects model and weighted means. Pooled results were compared between the treatment groups using χ^2-test and t-test (α= 0.05, two-sided).

In the analyses, five studies (n = 202 patients) were included in the exercise group and three studies (n = 470 patients) in the PTA group. Results demonstrated that at 3 and 6 months follow-up, ABI was significantly improved in the PTA group, but not in the exercise group. At 3 months, quality of life was significantly improved on the dimensions of physical functioning and bodily pain in the exercise group, and on the dimensions of physical role functioning and general health in the PTA group (Fig 2). Between the two treatment groups, ABIs were significantly different at 3 and 6 months, whereas mean change in quality-of-life scores was not significantly different during follow-up.[7] This review highlights the fact that there is limited information on long-term outcomes for exercise therapy.

It is well-recognized by vascular specialists that both percutaneous and open vascular therapies fail over time. This results in changes in quality of life over time, as well. Angioplasty of iliac or distal vessels for the treatment of claudication has a high likelihood of both technical and clinical success. The relatively low mortality and morbidity risk made PTA an established treatment option for patients with IC. It has 5-year patency rates of 80% for aortoiliac and 60% for femoropopliteal disease.[25–28]

There have been multiple studies that have documented the immediate and short-term quality-of-life benefits of successful percutaneous balloon angioplasty for treatment of claudication. Quality-of-life scores, using the SF-36 and Euro quality-of-life Health Assessment questionnaires, were recorded before and 1, 3, and 6 months after angioplasty in 108 claudicants treated with balloon angioplasty of causative iliac or SFA lesions. Improvements in the subscales and overall quality were noted by 1 month after treatment and were sustained at 6 months after intervention.[29] Similar findings were reported by Whyman and colleagues[30], who performed a randomized, prospective trial of angioplasty of short iliac or SFA lesions (n = 30) or medical treatment alone (n = 32) in a cohort of 62 claudicants. They evaluated these patients with clinical parameters of duplex imaging of occlusive disease, ABI, treadmill walking distance, and quality of life with the Nottingham Health Profile. At the time of 6-month follow-up evaluation, none of the patients treated with angioplasty reported symptoms of claudication. They had lower pain scores and overall improvement in quality of life as recorded by the Nottingham Health Profile survey compared to the control group who received medical therapy only. Of significance, the investigators reported on the status of these patients 2 years after treatment.[31] Although the angioplasty sites remained patent, there were no statistically significant differences in treadmill walking distance, patient-reported walking distance, ABI, or quality-of-life scores between the angioplasty and control groups.

These findings on the diminishing benefit on quality of life of angioplasty over time have been documented in many other studies. A Cochrane Database systematic review evaluated randomized trials of angioplasty for the treatment of mild or moderate claudication. This critical assessment of available data revealed that patients treated with angioplasty had neither a greater walking distance nor quality of life 2 years after intervention compared to patient controls.[32] This information suggests that angioplasty alone provides an immediate benefit, but the durability of the treatment, as measured by quality-of-life assessment, is limited. The amount of specific data on this point, though, is limited.

Surgical revascularization is infrequently warranted for treatment of the claudicant. The recently published American Heart Association guidelines[33] for management of claudication are in accord with those set forth in the TASC guidelines[4] and recommend surgical revascularization only for those individuals who have significant lifestyle or job-threatening limitations, and who have failed exercise and pharmacotherapy. Therefore, the quality of life of claudicants after bypass surgery has not been extensively studied.

Klevsgard and colleagues[34] reported the quality-of-life changes in 31 patients with IC who underwent successful revascularization and 9 patients in whom revascularization was unsuccessful. Using the Nottingham Health Profile and the SF-36 to document changes in quality of life, these investigators noted that those with successful surgery had improved scores in bodily pain, physical functioning, and vitality. None of these were improved in those with unsuccessful procedures.[34] In a recent study of 80 patients undergoing lower-extremity revascularization for treatment of claudication, the Nottingham Health Profile was used to assess health-related quality of life at 6 and 12 months after surgery and then up to 4 years postoperative. Improvement in scores of energy, pain, emotional reactions, and physical mobility were noted through 12 months. Improvements were maintained up to 4 years as long as the graft remained patent.[35]

These and other small studies have clearly established that quality-of-life improvements are associated with placement and maintenance of a patent bypass graft. The magnitude of the surgical endeavour, however, may impact upon this. Schneider and colleagues[36] evaluated the functional status and sense of well-being in 60 patients more than 6 months after placement of an aortobifemoral bypass graft. Although healing and postoperative recovery were complete, patients with functioning grafts had physical function, role function, bodily pain, and perceived health scores worse than those without symptomatic arterial disease. Graft failure may also result in significant or prolonged deterioration in perceived health and emotional status, as was noted by Ronayne in a small study of 25 patients.[37]

SUMMARY

Because the ultimate goal of healthcare is improvement in a patient's quality of life, this measure is one of the parameters by which the success of healthcare must be judged. There are many well-established and validated questionnaires that can ascertain, in a generic or disease-specific manner, quality of life and functional status as reported by the patient. When these instruments are applied to patients with IC, a significant impairment in functional status and quality of life can be clearly documented when compared to patients without PAD.

Treatment of those with claudication with any modality that can increase walking distance and reduce claudicationassociated pain can improve quality of life. This is true of exercise therapy, percutaneous procedures, or open surgery. Exercise therapy, when continued, has a durable benefit on patient quality of life and little associated inconvenience. Percutaneous and open revascularization procedures, when successful, provide immediate improvement in functional status for the claudicant. There is little quality-of-life data to document that improvement in quality of life with invasive procedures is sustained, but a growing body of information to suggest that quality of life and functional status begin to deteriorate over time. Further broad longitudinal studies will be required to better document the benefits of intervention in the claudicant.

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3 SYSTEMATIC REVIEW

INTERMITTENT CLAUDICATION: FUNCTIONAL CAPACITY AND QUALITY OF LIFE AFTER EXERCISE TRAINING OR PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY—SYSTEMATIC REVIEW

ABSTRACT

Purpose: To systematically review published data about the short- and long-term effects of exercise training and angioplasty on functional capacity and quality of life of patients with intermittent claudication.

Materials and methods: Articles published between January 1980 and February 2003 were included if patients had intermittent claudication treated with exercise training or angioplasty and if both functional capacity and quality-of-life scores from Medical Outcomes Study 36-Item Short Form health survey were reported for at least 3 months of follow-up. Data were pooled by using a random effects model and weighted means. Pooled results were compared between the treatment groups by using the χ^2-test and the Student t-test ($\alpha = .05$, two sided).

Results: In the analyses, five studies (202 patients) were included in the exercise group, and three studies (470 patients), in the angioplasty group. At 3 months of follow-up, the ankle-brachial index was significantly improved in the angioplasty group (mean change, 0.18; $p < .01$) but not in the exercise group (mean change, 0.01; $p = .29$). At 3 months, quality of life was significantly improved with regard to ratings of physical functioning and bodily pain in the exercise group (mean change, 18 and 10, respectively; $p < .01$) and physical role functioning in the angioplasty group (mean change, 30; $p = .03$). Mean change in ankle-brachial index significantly differed between the two treatment groups at 3 and 6 months ($p < .01$); mean change in quality-of-life scores did not.

Conclusion: Improvement in quality of life was demonstrated after both exercise training and angioplasty, whereas functional capacity showed significant improvement after angioplasty. The ankle-brachial index significantly differed between the two treatment groups at 3 and 6 months, whereas the quality-of-life scores did not.

INTRODUCTION

Intermittent claudication is the mildest manifestation (ie, Rutherford stage 1, 2, or 3) of peripheral arterial disease, and its prevalence is approximately 5% in men older than 50 years.[1,2] The overall aging of populations in Western societies indicates that the prevalence of this condition will increase over the next decades.[3] Various treatment strategies, such as exercise training and percutaneous transluminal angioplasty (PTA) with or without stent placement, have been proposed in order to ameliorate symptoms. The choice between exercise training and PTA in patients with intermittent claudication, however, has been the subject of controversy. To our knowledge, there has been no direct comparison of exercise training with PTA to determine the relative effects of these two therapies both on functional capacity (usually expressed as ankle-brachial index [ABI] or as walking distance) and on quality of life.

In 1957, Foley[4] described the beneficial effects of daily walks and physical training in patients with intermittent claudication. Several subsequent reports[5-7] confirmed that exercise training led to an improvement in the walking ability of patients with intermittent claudication. It has been shown to significantly improve both the onset of leg discomfort (initial walking distance) and the point at which the pain becomes unbearable and forces the patient to stop walking (maximum walking distance).[8,9] PTA became available in 1964 and is currently an established treatment option for patients with intermittent claudication.[10] Low complication rates (4%–5%) and 5-year patency rates of 80% for aortoiliac disease and 60% for femoropopliteal disease were reported for PTA.[11-14] This technique has been popularized as an inexpensive, effective, and simple method.[15-17]

In recent years, quality of life has been extensively used as a parameter for assessing and expressing the success of the outcome in patients with intermittent claudication.[18] The TransAtlantic Inter- Society Consensus stated that if quality of life could be accurately assessed, it would be the ideal primary end point.[19] Furthermore, the relationship between functional capacity and quality of life is complex and contradictory, and both therefore should be considered in the assessment of outcome.[20,21] There remains uncertainty surrounding the effectiveness of the treatment strategies in patients with intermittent claudication. Thus, the objective of our study was to systematically review the published data about the short- and longterm effects of exercise training and angioplasty on functional capacity and quality of life of patients with intermittent claudication.

MATERIALS AND METHODS

Data Sources and Data Extraction Publications were initially selected by the first author (S.S.), and the selection was verified by a coauthor (J.L.B.). The final selection was made by both authors together. Both authors evaluated all reports independently for inclusion and exclusion criteria.

A literature search was performed by using MEDLINE and the reference lists in articles. Further searches were performed by using the same keywords in the Cochrane Central Register of Controlled Trials, Cochrane Anesthesia Group Specialized Register, Cumulative Index to Nursing and Allied Health Literature, and PiCarta.

The reviewers used the English-language medical literature published in 1980 or later.[22] Published studies of PTA dated from 1980, and to find contemporary controls between the exercise group and the PTA group, we restricted our review to this period. Randomized controlled trials, prospective cohort studies, and retrospective cohort studies were included, while case reports and reviews were

excluded. Key words were ("intermittent claudication" OR "claudicants") AND ("angioplasty" OR "PTA" OR "stent placement" OR "balloon dilation" OR "exercise" OR "gymnastics" OR "walking" OR "training") AND ("quality of life" OR "QoL" OR "health status") AND ("functional capacity" OR "ankle brachial index" OR "walking distance") AND ("vascular peripheral" OR "arterial peripheral"). The studies were included if they met the following criteria: Patients with intermittent claudication were included and were treated with either exercise training (walking or gymnastics) or with PTA with or without stent placement in lesions in the aortoiliac or femoropopliteal arterial segments. Both functional capacity as demonstrated by walking distance (on a treadmill or as reported by the patient) or ABI, and quality-of-life scores (generic or disease specific) for at least 3 months of follow-up, were reported. Reports about PTA studies that also included patients with critical ischemia were excluded from our analysis if the outcome results were not reported separately for patients with critical ischemia and for those with intermittent claudication.[23,24] When the same group of investigators reported their results in various journals, all reports were examined for similarities and completeness, and the results were treated as those of a single study in our review.[25,26]

Data were abstracted independently by the same two authors who selected the publications. The following parameters were recorded: study design; patient characteristics; measures of severity of claudication, such as Rutherford classification, walking distance, and ABI; type of exercise training or intervention; outcomes; and follow-up results reported by using standardized forms. The exercise training programs were evaluated by the same two authors, and discrepancies between the evaluations were resolved with consensus.

Functional Capacity and Quality of Life

The ABI at rest and the maximum treadmill walking distance are the most frequently reported outcomes of functional capacity. The ABI is defined as the ratio of the systolic blood pressure measured at one of the ankle arteries to the systolic blood pressure measured at the brachial artery.[9] The most efficient and reliable test for the determination of the maximum walking distance is considered to be a treadmill test.[27]

The Medical Outcomes Study 36-Item Short Form (SF-36) health survey was most frequently used in studies in which investigators evaluated quality of life after exercise training or PTA in patients with intermittent claudication. The SF-36 survey was developed to evaluate the physical, social, and physical role functioning of patients and to elicit their perceptions of their general health and well-being in eight dimensions.[28] Each dimension is subjectively rated by the respondent and assigned a score on a scale of 0–100 in which 100 indicates best functioning or well-being. In previous studies, it was demonstrated that the dimensions of physical functioning, bodily pain, and physical role functioning showed the most substantial improvement after treatment in patients with intermittent claudication.[29] In this study, therefore, we concentrated on the following three dimensions: physical functioning (limitation of usual activities because of a physical problem), physical role functioning (limitation of usual role activities because of a physical problem), and bodily pain (pain or discomfort in the body). In addition, we added the dimension of general health. If data from the SF-36 survey were not reported but data from SF-20 (a shorter version of the same survey) were available, the SF-20 data were used. For studies of exercise training, data beyond 6 months of follow-up were not available, and for studies of PTA, data at 6 months were poor. The weighted means for functional capacity and the quality-of-life scores in the PTA studies did not change significantly between 3 months and 12 months of follow-up. Therefore, to improve the comparison between the exercise training and PTA studies at 6 months of follow-up, we used the data obtained at 12 months of follow- up to calculate the weighted means at 6 months.

Statistical Analysis of Data

To pool data for discrete variables such as male sex, cardiac disease, hypertension, diabetes mellitus, pulmonary disease, hyperlipidemia, stroke, history of smoking, and current smoking, the random effects model described by Laird and Mosteller[30] was used. The random effects model takes into account the variance between studies, as well as that within studies. Because of the lack of reported data for variance around the means of continuous variables such as age, ABI, walking distance, and quality-of-life score, we were unable to use the random effects model to pool the continuous variables. Therefore, we calculated the weighted mean and 95% confidence interval (CI) for these variables.

Within the treatment study groups of exercise and PTA, the dichotomous baseline characteristics of all patients in the included studies were tested for homogeneity by using the χ^2-test (statistical significance level, $\alpha = .05$). Differences in pooled patient characteristics between the studies of PTA and those of exercise were tested with the χ^2-test and with the paired (two-sample) Student t-test (statistical significance level, $\alpha = .05$, two sided).

Improvements in functional capacity and quality of life between baseline and 3 months of follow-up and between baseline and 6 months of follow-up within the exercise study group and within the PTA study group were calculated and tested for statistical significance (paired Student t-test, $\alpha = .05$).

A funnel plot was constructed to detect the presence of publication bias (i.e. bias resulting from the greater likelihood of publication for studies reporting a positive result than for studies reporting a negative result).[31] In the current study, we plotted the number of patients who underwent exercise training or PTA as a function of the mean change in physical functioning (i.e. baseline data vs data at 3 months of follow-up [or 6 months of follow-up, if 3-month follow- up data were unavailable]). If there is no publication bias, the distribution of the data points will be symmetric and shaped like an inverted V.

The analyses were performed with software (Excel, release 2003, Microsoft Corporation, Redmond, Wash; SPSS, release 11.0.1, SPSS, Chicago, Ill).

RESULTS

Selected Articles and Comparisons

From the literature search, a total of 380 abstracts published between January 1980 and February 2003 were selected. Many studies ($n = 348$) were excluded on the basis of the abstract for the following reasons: There was no relation with peripheral arterial disease ($n = 191$); drug use in patients with intermittent claudication was investigated ($n = 78$); only patients with ischemia were included in the study ($n = 23$); patients with both intermittent claudication and ischemia were included in the study, without differentiation according to disease severity in the reported results ($n = 2$); or the follow-up period was shorter than 3 months ($n = 54$). Of the remaining 32 studies, 22 were excluded because patient characteristics were missing ($n = 5$), no data on both functional capacity and quality of life were reported ($n = 16$), or dichotomous outcomes were used for walking distances ($n = 1$). Of the 10 eligible articles, two[25,26] reported data from the same study population and were therefore considered as one study. All publications from studies that met our selection criteria reported either SF-36 or SF-20 survey data, with two exceptions: In one article[32], data from the Nottingham Health Profile questionnaire were reported, and in another article[33], data from a disease-specific questionnaire, PAVK-86,

were reported instead. To improve the comparison of quality-of-life scores between the studies, we excluded these two studies from our systematic review. Thus, seven studies[12,25,26,34–38] with a total of 202 patients who underwent exercise training therapy and 470 patients who underwent PTA (Tables 1 and 2) were included in our review.

Four of the seven studies were randomized controlled trials (Table 1). However, in none of these randomized controlled trials was exercise training compared with PTA directly: In one study, primary stent placement was compared with primary PTA, and in three randomized controlled trials, different types of exercise training were compared. The remaining three studies were prospective cohort studies; in one of these, exercise training and PTA were compared. Follow-up periods varied from 3 to 24 months; in only one study was the mean follow-up period (14.7 months) reported.[12]

Many baseline demographic and patient characteristics were not reported (Table 3). The percentage of male patients was 69% in the exercise training group and 73% in the PTA group ($p = .56$). The mean age of patients in the exercise training group also was not significantly different from that in the PTA group (68 vs 63 years, respectively; $p = .33$).

Across the studies in each treatment group, homogeneity was found in the proportion of the study population with male sex, coronary artery disease, hypertension, pulmonary disease, hyperlipidemia, stroke, and smoking behavior. Among the studies in the exercise training group, heterogeneity was found in regard to the percentage of patients with diabetes mellitus and the percentage of patients who were current smokers. Among the studies in the PTA group, no heterogeneity was found for these comorbidities.

Between the two treatment groups, patient characteristics were similar, except in regard to the percentages of patients with hypertension and stroke, which were significantly higher in the exercise training group than in the PTA group (64% vs 31%, $p = .01$, for hypertension; 23% vs 11%, $p = .03$, for stroke).

The weighted mean ABI at baseline in the exercise training group was lower than that in the PTA group (0.64 vs 0.71), but the difference was not statistically significant ($p = .13$). Also, no statistically significant difference was found in the weighted mean for maximum walking distance at baseline between the exercise training group and the PTA group (289 m vs 155 m, respectively; $p = .11$).
To detect publication bias, we constructed two funnel plots: one for the PTA group, and one for the exercise training group. Neither plot appeared symmetric. There were too few studies, however, to permit a proper evaluation of publication bias.

Exercise Training Programs

The exercise training programs differed across the studies (Table 4). These differences included variations in supervision, intensity, frequency, duration, and type of exercise. Of the five studies included in the exercise training group, one study involved supervised training, one study involved unsupervised training, and three studies each included one group with supervised training and one group with unsupervised training. Supervision implied that patients participated in a structured hospital-based exercise program.

In all programs, the frequency of supervised exercise training was at least three times per week, and walking was the mode of exercise used. In addition to walking, one study used a combination of

Table 1: Characteristics of Studies of Exercise Training or PTA for Intermittent Claudication

Study and Reference	Year of Publication	Study Location	No. of Institutions	Study period*	Treatment	Type of Study	Quality-of-Life Data Collection†
Bosch et al[12]	1999	The Netherlands	6	1993-1996	PTA	Prospective cohort and randomized controlled trial‡	SF-36, EuroQol-5D, HUI, rating scale, time trade-off, standard gamble
Chetter et al[25, 26]	1998 - 1999	England	1	1994-1996	PTA	Pros cohort	SF-36, EuroQol-5D
Currie et al[34]	1997	England	1	1993-1994	PTA & Exercise	Pros cohort	SF-36
Gardner et al[35]	2001	United States	1	ND	Exercise	Prospective cohort and randomized controlled trial§	SF-36
Patterson et al[36]	1997	United States	1	ND	Exercise	Pros cohort	SF-36
Regensteiner et al[37]	1997	United States	1	ND	Exercise	Prospective cohort and randomized controlled trial|	SF-20, WIQ
Savage et al[38]	1997	United States	1	ND	Exercise	Prospective cohort and randomized controlled trial#	SF-36

* ND no data.
† For a description of time trade-off and standard gamble (preference measures), see reference 44. EuroQol-5D five-dimensional quality-of-life survey developed by EuroQol Group, HUI Health Utilities Index, SF-20 Medical Outcomes Study 20-Item Short Form, WIQ Walking ImpairmentQuestionnaire.
‡ Comparison between primary stent placement and primary angioplasty with subsequent selective stent placement.
§ Comparison between exercise rehabilitation group and nonexercise (control) group.
| Comparison between supervised hospital-based exercise program and unsupervised home-based exercise program.
Comparison between supervised exercise program and home-based exercise program.

Table 2: Criteria for Inclusion or Exclusion of Patients in Each Study

Study	Inclusion criteria	Exclusion criteria
Bosch et al[12]	Intermittent claudication or critical ischemia caused by stenosis or occlusion in the iliac arteries	Stenosis of more than 10 cm in length; arterial occlusion of more than 5 cm, or of 5 cm or less in length and not allowing the passage of a guidewire; stenosis involving the distal aorta; severe comorbidity (eg, severe cardiac or cerebrovascular abnormality, malignant disease); and nonmedical factors such as inability to understand Dutch, or expected poor compliance
Chetter et al[25]	Treatment with PTA for intermittent claudication	Critical ischemia as defined by the European Consensus document
Curie et al[34]	Intermittent claudication and lower limb arterial disease potentially suitable for vascular intervention	Not reported
Gardner et al[35]	Positive response on Rose et al (45) questionnaire, age 60 years, ABI 0.97	Fontaine stage I or III disease; exercise tolerance limited by factors other than claudication; poorly controlled hypertension; pulmonary disease; hemiparetic gait; severe arthritis; poorly controlled diabetes mellitus; active major medical problem, including cancer, renal or liver disease, anemia, substance abuse, and dementia
Patterson et al[36]	Symptoms 3 months, ABI 0.9 at rest, or systolic blood pressure decrease of 15 mm Hg or more after exercise test	Ischemic rest pain or tissue loss, inability to participate in an exercise program because of limitations of comorbid illness, failed cardiac screening
Regensteiner et al[37]	Stable intermittent claudication 3 months; ABI 0.94 at rest, decreased to 0.73 after exercise test	Pain at rest, no ischemic ulceration or gangrene, inability to walk on the treadmill at a speed 2 mph, symptoms of angina, congestive heart failure, chronic obstructive pulmonary disease, arthritis, diabetes, previous vascular surgery or angioplasty within previous year
Savage et al[38]	Age 50 years; Rutherford stage I, II, or III disease; unilateral intermittent claudication	Unstable cardiopulmonary disease; severe extremity arthritis; tobacco use; weight 40 kg above ideal; renal insufficiency; use of beta-blocker, pentoxifylline, or cilostazol within 8 weeks of entry; functioning lower extremity bypass; severe cognitive impairment

Note.—PTA = Percutaneous Transluminal Angioplasty, IC = Intermittent Claudication, ABI = Ankle Brachial Index

Table 3

Study, Reference, and Patient Group	No. of Patients	Male Sex (%)	Age (y) *	Cardiac Disease (%)	Hypertension (%)	Diabetes Mellitus (%)	Pulmonary Disease (%)	Hyperlipidemia (%)	Stroke (%)	History of Smoking (%)	Current Smokers (%)	ABI at Rest	Maximum Treadmill Walking Distance (m)	No. of Lesions	Site of lesion†		
															Aortoiliac Arteries	Femoropopliteal Arteries	Both
Exercise Training Studies																	
Currie et al group 1[34]	78	76	68‡	41	ND	10	ND	ND	ND	ND	ND	0.65	ND	ND	ND	ND	ND
Gardner et al[35]	28	89	71	50	82	46	18	64	21	ND	ND	0.68	396	ND	ND	ND	ND
Patterson et al[36]																	
Group 1	27	59	67.9	41	70	29.6	ND	ND	ND	91	26	0.57	145	ND	ND	ND	ND
Group 2	28	46	70.3	39	54	39.3	ND	ND	ND	75	21	0.59	145	ND	ND	ND	ND
Regensteiner et al[37]																	
Group 1	10	ND	65	30	50	0§	ND	40	30	ND	60	0.64	245	ND	ND	ND	ND
Group 2	10	ND	64	30	50	0§	ND	30	20	ND	50	0.56	331	ND	ND	ND	ND
Savage et al[38]																	
Group 1	10	70	66.1	60	ND	ND	ND	ND	ND	ND	0§	0.57	532.2	ND	ND	ND	ND
Group 2	11	73	66.4	64	ND	ND	ND	ND	ND	ND	0§	0.71	52.5	ND	ND	ND	ND
All of the above	202																
Mean‖	NA	69.0	68.2#	43.3	64.0**	21.7	18.0	48.4	22.7**	82.9	26.0	0.64#	289.3#	ND	ND	ND	ND
95% CI	NA						NA							ND	ND	ND	ND
Lower limit		57.8	64.5	35.7	52.1	3.5		29.0	21.1	58.5	6.0	0.54	0.04				
Upper limit		80.3	71.9	50.8	75.9	39.8		67.7	97.5	107.3	46.0	0.74	578.7				
PTA																	
Bosch et al[12]																	
Group 1	143	71	59	ND	28	9	ND	24††	14	87	ND	0.74	190	187	187	0	0
Group 2	136	73	60	ND	27	11	ND	26††	7	94	ND	0.73	204	169	169	0	0
Chetter et al[25]	117	78	67‡	30	37	14	20	20	13	ND	58	0.65	56	82	24	39	19
Currrie et al group 2[34]	74	72	73‡	30	ND	14	ND	ND	ND	ND	ND	0.70	ND	85	31	54	0
All of the above	470													523	411	93	19
Mean‖	NA	73.3	63.5#	30.0	30.5**	11.4	20.0	23.0	11.3**	90.4	58.0	0.71#	155.2#	NA	NA	NA	NA
95% CI	NA			NS			NA				NA			NA	NA	NA	NA
Lower limit		70.6	53.3		24.3	9.2		19.0	7.0	79.4		0.64	28.6				
Upper limit		76.1	73.7		36.7	13.5		28.0	15.6	101.4		0.78	281.8				

Note.—Data are in patients unless otherwise specified. NA not applicable, ND no data., * Data are mean unless otherwise indicated., † Data are numbers of lesions., ‡ Median is given., § Current smoking or diabetes mellitus was an exclusion criterion., || Based on random effects model, except where otherwise indicated., # Weighted mean is given., ** A statistically significant difference (P< .05) was found between pooled mean for exercise training study group and pooled mean for PTA study group., †† Values obtained from Tetteroo et al.[46]

Table 4: Components of Exercise Training Programs for Patients with Intermittent Claudication in the Included Studies

Study, Reference, and Patient Group	Supervision	Mode of Exercise	Treadmill Exercise Speed and Grade	Frequency of Exercise (d/wk)	Duration of Exercise Session (min)	Length of Exercise Training Program (wk)	Mean Compliance (%)
Currie et al[34], group 2	no	Different exercises while lying, sitting, and standing, and daily walking	No treadmill used	7	ND	12	92*
Patterson et al[36], group 2	No; weekly lectures, instruction, and logs	walking	No treadmill used	3	20-40	12	78*
Regensteiner et al[37], '97group 2	No; weekly contact by telephone	walking	No treadmill used	3	35-50 (including rest periods)	12	100
Savage et al[38], group 2	No; contact by telephone once a month	Walking to point of intense pain	No treadmill used	3	15-40	24	ND
Gardner et al[35]	yes	Treadmill walking to near claudication pain	2 mph, 0% grade with 2% increase every 2 min until maximal claudication pain	3	ND	24	73
Patterson et al[36], group 1	Yes, with weekly lectures	Arm and leg ergometry, stationary cycling	1–2 mph, 2%–3% grade	3	60	12	78*
Regensteiner et al '97[37], group1	yes	walking	2 mph, 0% grade for 3 min, increased to 3.5% grade every 3 min to maximal claudication pain	3	35-50 (including rest periods)	12	100
Savage et al[38], group 1	yes	walking	2 mph, 0% grade with 2% increase every 2 min until maximal claudication pain	3	15-40	24†	ND

Note.—ND no data.

* Mean compliance for both groups (1 and 2) is given.

† After 12 weeks, patients in the hospital exercise program were transferred to the home exercise program.

walking, standing on tiptoe, and cycling.[33,36] The duration of the supervised exercise training session varied from 15 to 60 minutes. The duration of the exercise training programs varied from 12 to 24 weeks. The mean percentage of compliance among patients in the supervised programs varied from 73% to 100%. (In one study, compliance was not reported.)

In the four unsupervised programs, the type and intensity of contact with the patient varied from weekly or monthly conversations by telephone to weekly lectures and instructions or to no contact during the exercise program. In one study, patients were asked to maintain a weekly log. The mean compliance of the patients in the unsupervised programs varied from 78% to 100% (in one study, compliance was not reported).

Functional Capacity

All studies reported the ABI during rest at baseline (Table 5). The maximum walking distance was determined in two of the three studies in the PTA group and in four of the five studies in the exercise training group. It should be noted that the test duration and the speed and grade settings used during the treadmill test to determine the maximum walking distance varied between studies. Grades of 0%–10% were used with speeds of 1–2 mph (1.6–3.2 km/h), either fixed or increased in increments of 1 or 2 mph.

In the exercise training group, 1- or 2-year follow-up data were not available (Table 5). Improvement was shown in the mean ABI at rest between baseline and 3- or 6-month follow-up, but the difference was not statistically significant ($p = .29$ and $p = .73$, respectively) (Fig 1). At 3 months, there was no statistically significant improvement in the mean maximum walking distance ($p = .09$), but a statistically significant improvement in the mean maximum walking distance was demonstrated between baseline and 6-month follow-up ($p = .02$).

In the PTA group, a significant improvement in the mean ABI at rest was demonstrated at 3 and 6 months of follow- up ($p < .01$ for both) (Fig 1). In addition, a statistically significant improvement in the mean maximum walking distance was demonstrated at 3 months ($p = .01$) and 6 months ($p < .01$). The difference between the two treatment groups in ABI at 3 and 6 months was significant ($p < .01$ and $p = .02$, respectively). Although the weighted means of the maximum walking distance at baseline were not significantly different between the treatment groups, we did not compare this outcome of functional capacity during follow-up, because of the variation in measurements of the maximum walking distance among the studies.

Quality of Life

In the exercise training group, the mean scores for the dimensions of physical functioning, physical role functioning, bodily pain, and general health demonstrated improvement at 3 and 6 months (Fig 2, Table 6). However, the improvement was statistically significant only for the dimensions of physical functioning and bodily pain at 3 months and for the dimension of bodily pain at 6 months. The effect of treatment was highest for the dimension of physical functioning at 3 months ($p < .01$).

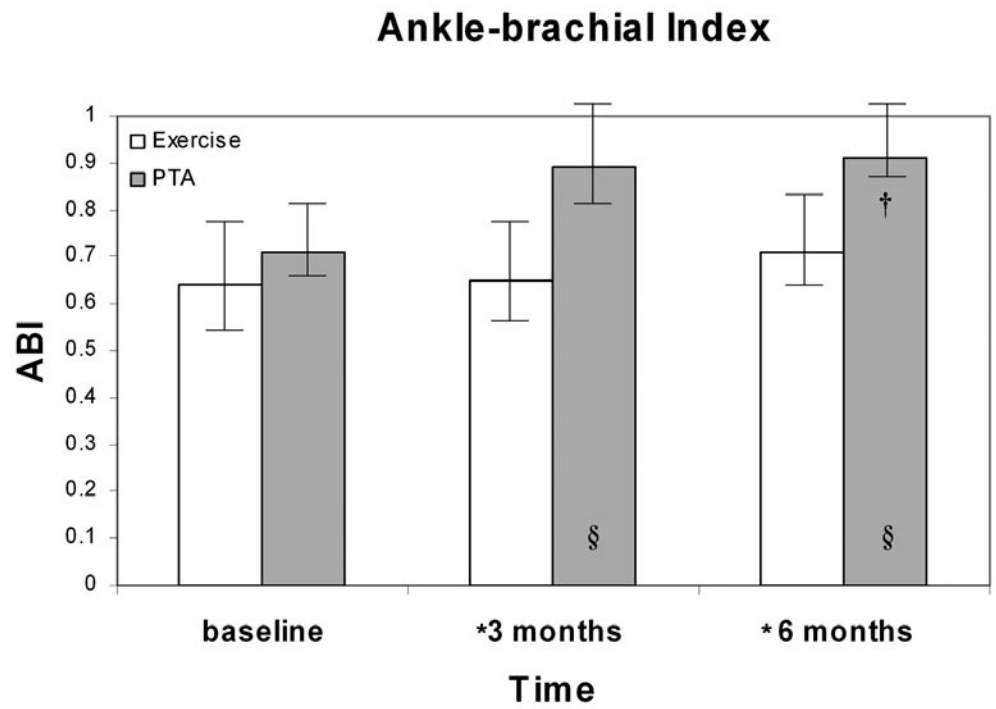
In the PTA group, mean scores for the dimensions of physical functioning, physical role functioning, bodily pain, and general health showed improvement at 3 and 6 months. Improvements were statistically significant for the dimensions of physical role functioning and general health at 3 months (Fig 2, Table 6). The effect of treatment was greatest for the dimension of physical role functioning after 3 months ($p < .01$).

Table 5: Functional Capacity in the Exercise Training and PTA Study Groups at Baseline and during Follow-up

			Follow-up			
	Baseline		3 months		6 months	
Study, Reference, and Patient Group	ABI rest	Maximum Treadmill Walking Distance (m)	ABI rest	Maximum Treadmill Walking Distance (m)	ABI rest	Maximum Treadmill Walking Distance (m)
Exercise Training Studies						
Currie et al[34] Group 1	0.65	ND	0.64	ND	ND	ND
Gardner et al[35]	0.68	396	ND	ND	0.67	702
Patterson et al[36]						
Group 1	0.57	145	ND	ND	ND	ND
Group 2	0.59	145	ND	ND	ND	ND
Regensteiner et al[37]						
Group 1	0.64	245	0.63	ND	ND	ND
Group 2	0.56	331	0.53	ND	ND	ND
Savage et al[38]						
Group 1	0.75	532	0.76	763.5	0.71	742
Group 2	0.71	521	0.71	833.3	0.81	715
All of the above						
Weighted mean	0.64	289	0.65	787	0.71	713
95% CI						
Lower limit	0.54	-0.04	0.55	690	0.62	682
Upper limit	0.74	579	0.75	884	0.80	744
PTA Studies						
Bosch et al[12]						
Group 1	0.74	190	0.92	263	0.92*	261*
Group 2	0.73	204	0.93	255	0.94*	263*
Chetter et al[25]	0.65	56	0.88	111	0.87*	125*
Currie et al Group 2[34]	0.70	ND	0.81	ND	ND	ND
All of the above						
Weighted mean	0.71	155	0.89	215	0.91*	222*
95% CI						
Lower limit	0.64	29	0.89	83	0.87	99
Upper limit	0.78	282	0.90	348	0.95	344

Note.—ND no data.
* Twelve-month follow-up values.

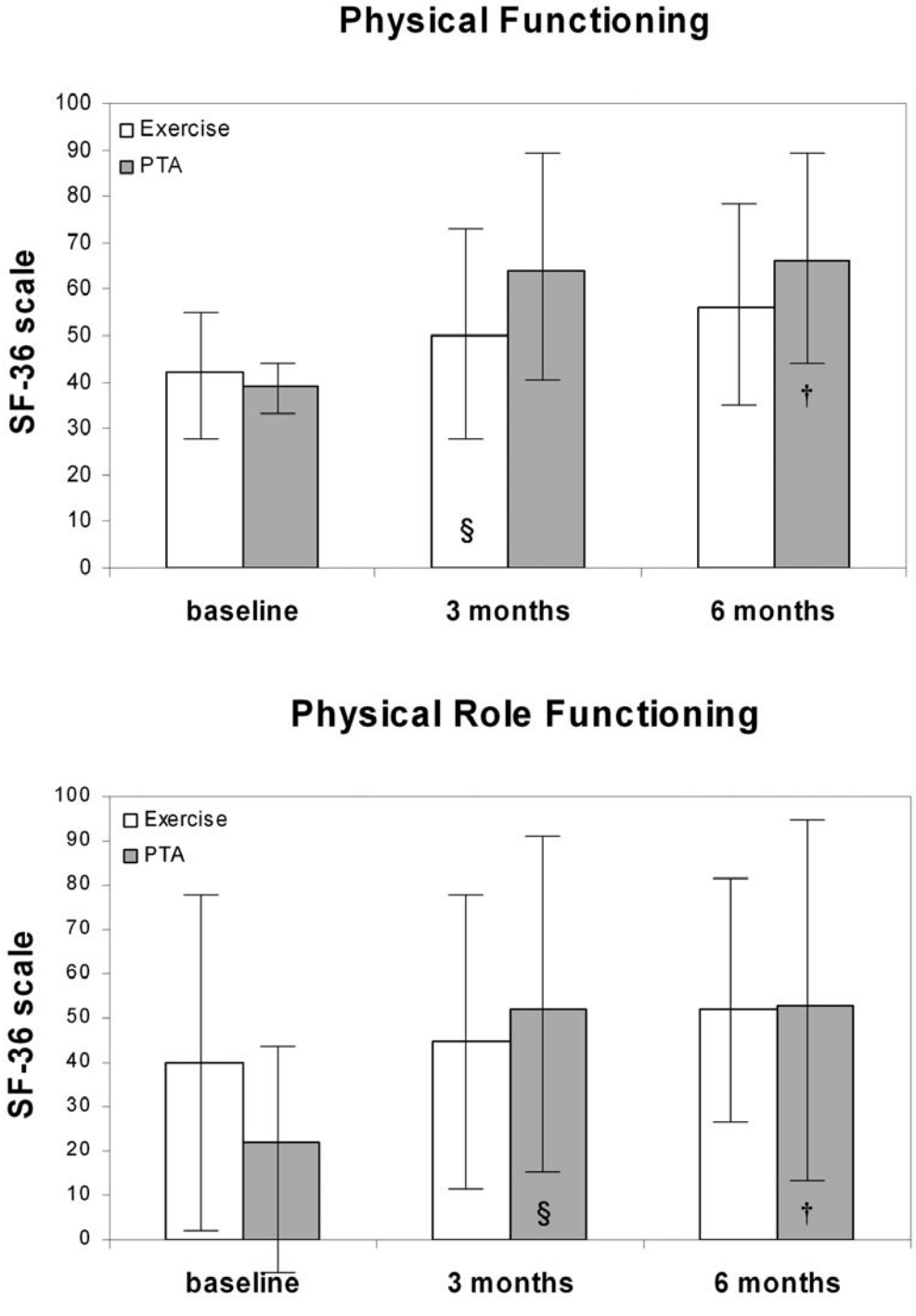
Figure 1. Weighted means and 95% CI of Ankle-brachial Indices for the exercise training and PTA group at baseline and during follow-up

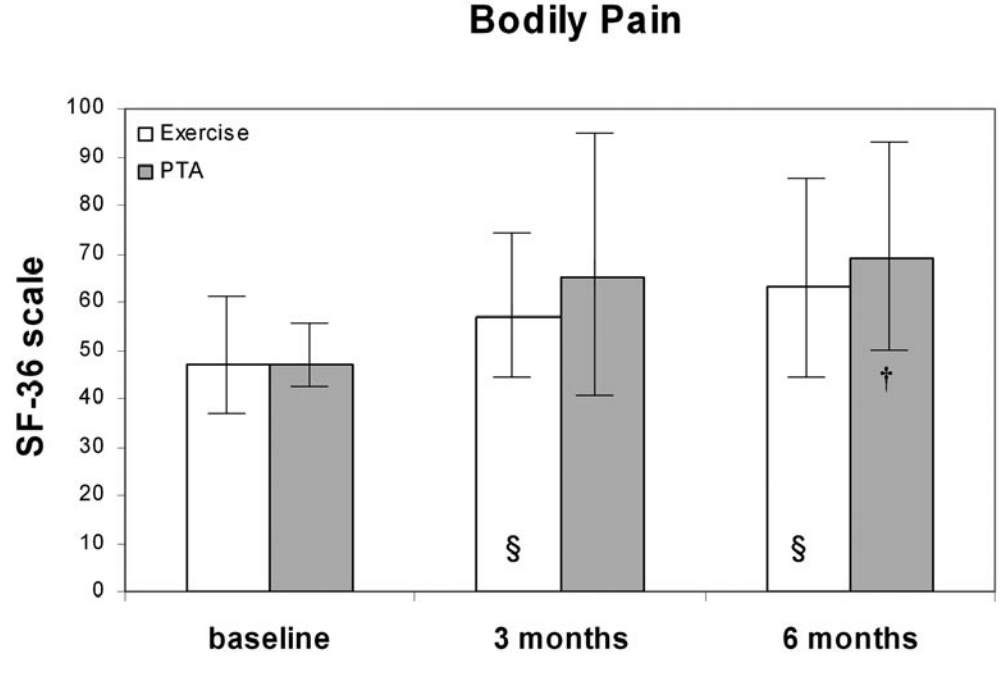


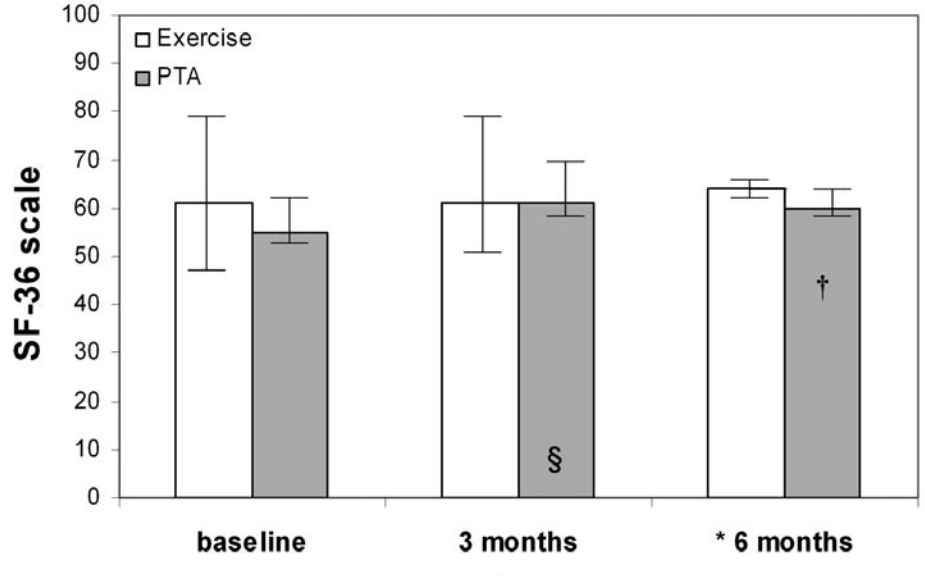
* Significant difference between the two groups.
† If 6 months values were not available, the 12 months values were used.
§ Significant improvement in group during follow-up.

There were no significant differences at baseline between the two treatment groups with regard to the dimensions of physical functioning, physical role functioning, bodily pain, and general health. In addition, no significant differences in the mean change of quality of life were demonstrated between the two treatment groups during follow-up.

Figure 2. Weighted means and 95% CI of SF-36 dimensions for the exercise training and PTA group at baseline and during follow-up.







* Significant difference between the two groups.
† If 6 months values were not available, the 12 months values were used.
§ Significant improvement in group during follow-up.

Table 6: Quality of Life in Exercise Training and PTA Study Groups at Baseline and during Follow-up

Study, Reference, and Patient Group	baseline				3 months				6 months			
	PF	PRF	BP	GH	PF	PRF	BP	GH	PF	PRF	BP	GH
Exercise Training Studies												
Currie et al[34] Group 1	36	26	42	ND	39*	31*	49*	ND	ND	ND	ND	ND
Gardner et al[35]	41	ND	ND	ND	ND	ND	ND	ND	41	ND	ND	ND
Patterson et al[36]												
Group 1	43	45	53	64	52	44	64	65	56	49	62	64
Group 2	41	30	51	60	53	49	61	62	54	45	64	64
Regensteiner et al[37]												
Group 1	52	65	ND	45	72	63	ND	56	ND	ND	ND	ND
Group 2	61	65	ND	50	71	66	ND	40	ND	ND	ND	ND
Savage et al[38]												
Group 1	54	84	59	71	60	77	70	64	56	84	65	66
Group 2	45	47	50	67	61	68	72	65	54	47	64	65
All of the above												
Weighted Mean	42	40	47	61	50	45	57	61	56	52	63	64
95% CI												
Lower limit	29	6	36	46	28	15	40	46	36	27	61	63
Upper limit	55	74	58	75	71	74	73	75	77	77	66	66
PTA Studies												
Bosch et al[12†]												
Group 1	40	27	50	57	74	67	78	63	70‡	62‡	75‡	60‡
Group 2	42	32	49	53	74	64	74	58	76‡	68‡	75‡	59‡
Chetter et al[26§]	35	2	44	ND	50	25	44	ND	50	25	56	ND
Currie et al[34] Group 2	38	27	41	ND	50*	46*	58*	ND	ND	ND	ND	ND
All of the above												
Weighted Mean	39	22	47	55	64	52	65	61	66	53	69	60
95% CI												
Lower limit	34	-1	40	51	41	19	38	56	45	17	52	59
Upper limit	44	45	54	59	87	86	92	66	87	89	86	61

Notes.—Unless otherwise specified, data are mean values from ratings on a scale of 0–100, with 0 indicating worst health and 100 indicating perfect health. BP bodily pain, GH general health, ND no data, PF physical functioning, PRF physical role functioning.

* Values are medians obtained from Chetter et al [26] for the same study population.

† Values were obtained from Klein et al [47] for patients in the Dutch Iliac Stent Trial.

‡ Values were obtained at 12-month follow-up.

§ Values are medians.

DISCUSSION

In the current systematic review, functional capacity and quality-of-life outcomes after exercise training or PTA were reviewed and compared. Results demonstrated that at 3 and 6 months of follow- up the ABI was significantly improved in the PTA group but not in the exercise group. Quality of life was significantly improved in the dimensions of physical functioning and bodily pain in the exercise group and in the dimensions of physical role functioning and general health in the PTA group at 3 months. ABI significantly differed between the two treatment groups at 3 and 6 months, whereas the mean change in the quality-of- life scores did not significantly differ between the groups during follow-up.

To our knowledge, no review has been published in which exercise training and PTA are compared with regard to both functional capacity and quality of life. In addition, results have been published from only two randomized controlled trials in which exercise training and PTA were directly compared.[32,39] These studies, however, did not meet our inclusion criteria; one study did not report both functional capacity and quality of life, and the other study did not use the SF-36 survey for quality-of-life assessment. The results of one of these studies showed that, at 12 months of follow-up, patients with mild or moderate intermittent claudication who underwent supervised exercise training had greater symptomatic improvement than did patients who underwent PTA.[39] Results of the other study showed no significant difference in quality of life between control subjects (patients after unsupervised exercise training) and the PTA group after 2 years of follow-up.[32,40] The PTA group, however, included substantially fewer patients with arterial occlusion and/or severe stenosis than did the exercise group. Data from these two randomized controlled trials were collected for a review, but the trials were relatively small, and the results must be interpreted with caution.[41]

Unfortunately, one of the limitations in our systematic review was that data for both functional capacity and quality of life were inconsistently reported. In particular, data about long-term functional capacity and quality-of-life outcomes for exercise training after 6 months were lacking, and, in consequence, the deleterious effect of postangioplasty restenoses must have been somewhat underestimated. Furthermore, many baseline demographic and patient characteristics that may have been relevant to a comparison between treatment groups, such as the disease location (aortoiliac vs femoropopliteal arteries), smoking history, and the use of medications (eg, cilostazol, statins), were not reported.

Another limitation, which became apparent after review of the exercise training programs, is the lack of standardization in the different components of exercise training. This limitation hampered the comparison of the reported results of the different studies. Investigators in the different exercise training studies evaluated the effectiveness of supervised or unsupervised exercise programs, but the relative effectiveness of these programs is still controversial. Some studies, particularly those performed in Europe, have shown good results with a home-based exercise program.[42,43] Other studies, however, have shown little benefit for this type of program,[37] whereas supervised exercise has provided consistent clinical improvement in almost every study.[8,36–38] There is also a lack of standardization of the treadmill test with regard to the use of fixed loading or graded loading, different speeds, and different maximum walking times. A longer walking distance was used in the exercise studies than in the PTA studies. These different protocols could help to explain the different maximum walking distances reported at baseline and during follow-up between the two treatments. The existence of this bias hampered comparison between the two treatments.

Another limitation of our study was the potential publication bias. However, studies in the exercise training group were relatively small, and there were only four studies in the PTA group, which limits power for detection of publication bias. Another limitation of the current systematic review is that the included studies were not randomized controlled trials in which exercise training was compared with PTA. This implies that the population undergoing exercise training may differ from the population undergoing PTA. Nevertheless, in our study, most patient characteristics were not significantly different between the treatment groups. Even though randomized controlled clinical trials are supposed to be the superior mode for evaluating and comparing different treatment modalities, they too have limitations.[44] In general, a randomized trial is performed in an ideal setting, with a selected, usually small, patient population, which may hamper generalization of the results. Systematic reviews of cohort studies, on the other hand, may reflect general clinical practice and provide additional data about a larger number of patients.

There is still no evidence that quality of life for patients with intermittent claudication is significantly better after PTA than after exercise training after more than 6 months. Patients with intermittent claudication are often treated conservatively; however, various exercise training programs are used.[34–38] In addition, the definitions of supervised exercise and unsupervised exercise vary widely in European countries. Therefore, a standardized exercise training program with measurement of the maximum walking distance according to a universally accepted standard would be desirable. Over the past decade, PTA has been more widely used in patients with intermittent claudication, mainly because of its low associated morbidity and mortality.[11–13] PTA, however, is a local form of treatment, and it is therefore not surprising that patients may experience relapse after PTA, with ipsilateral or contralateral symptoms representing progressive disease at other sites; the benefit with PTA may be a short-term effect. A randomized controlled trial of both treatments with long-term follow-up will enable further evaluation of effectiveness and determination of functional capacity and quality of life after more than 6 months.

In conclusion, our results demonstrate an improvement in quality of life after exercise training, whereas both functional capacity and quality of life showed significant improvement after PTA. ABIs in the PTA group were significantly higher than those in the exercise training group at 3 and 6 months, whereas the mean change in quality-of-life scores was not significantly different between the two groups during follow-up. Despite the limitations outlined, our analysis has shown the best evidence that we have. This is what we know at this point in time, and more needs to be done.

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4 CLINICAL EFFECTIVENESS FOLLOWING TREATMENT OF INTERMITTENT CLAUDICATION: A RANDOMIZED CONTROLLED TRIAL

ENDOVASCULAR REVASCULARIZATION VERSUS SUPERVISED HOSPITAL-BASED EXERCISE TRAINING FOR INTERMITTENT CLAUDICATION: CLINICAL EFFECTIVENESS IN A RANDOMIZED CONTROLLED TRIAL

ABSTRACT

Purpose: To compare clinical success, functional capacity, and health-related quality of life during 12-months follow-up after endovascular revascularization or supervised hospital-based exercise training in patients with intermittent claudication.

Materials and methods: Between September 2002-September 2005, we randomly assigned 151 consecutive patients, with intermittent claudication, to receive either endovascular revascularization -angioplasty-first approach- (n=76) or hospital-based supervised exercise (n=75). The outcome measures were clinical success, functional capacity, and health-related quality of life after 6- and 12-months. Significance of differences between the groups was assessed using the unpaired t-test, χ^2-test, or the Mann-Whitney U-test. We performed multivariable regression analysis to adjust outcomes for imbalances of baseline values

Results: Immediately after the start of treatment, revascularization patients improved more than exercise patients in clinical success (OR 39; 95% CI 15-98, p<0.001), but this advantage was lost after 6- and 12-months (OR 1.2; 95% CI 0.5, 2.5, p = 0.70 and OR 0.9; 95% CI 0.4, 1.7, p = 0.73 respectively). After revascularization, fewer patients exhibited ipsilateral symptoms at 6 months compared to exercise (37% vs 69%; OR 0.4; 95% CI 0.2, 0.7, p < 0.001), but no significant differences were demonstrated at 12 months. After both treatments, functional capacity and quality-of-life scores increased after 6- and 12-months; however, only the maximum pain-free walking distance after 6 months was significantly different between the treatment groups (exercise group higher; a mean difference 16 meters; 95% CI 2, 29 meters, p = 0.02). No other outcomes, and no outcomes at 12 months, demonstrated significant differences.

Conclusion: The results demonstrate that after 6- and 12-months patients with intermittent claudication benefited equally from either endovascular revascularization or supervised hospital-based exercise. Improvement is, however, more immediate following revascularization.

INTRODUCTION

Intermittent claudication (i.e., Rutherford category 1, 2, or 3) is the most common clinical manifestation of peripheral arterial disease.[1,2] The prevalence varies from 3% to 6% in patients aged 40 to 60 years.[3] As Western society ages, the incidence of intermittent claudication is expected to increase, making questions related to its treatment pertinent.[4]

Larsen and Lassen[5] were the first to recommend exercise training for the treatment of intermittent claudication. Exercise training is also recommended as the initial treatment in the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease of 2007 (TASC II).[3] Endovascular revascularization, however, is becoming more common, presumably because it provides immediate benefit and therefore may prevent 'unnecessary disability'.[3]

This randomized controlled trial aimed to compare clinical success, functional capacity, and health-related quality of life during 12-months follow-up after endovascular revascularization or supervised hospital-based exercise training in patients with intermittent claudication.

METHODS

This trial was a single-center randomized controlled trial, in which the clinical effectiveness of primary endovascular revascularization was compared to supervised hospital-based exercise training as the initial treatment for patients with intermittent claudication (Rutherford category 1, 2, or 3). The study was conducted within the context of a large community hospital. We adhered to the guidelines for Good Clinical Practice, and the trial was registered under number ISRCTN 64443682.[6] Study data were analyzed and reported in accordance with the CONSORT guidelines.[7] The study was approved by the Institutional Review Board, and all patients gave written informed consent.

PATIENTS

From September 2002 to September 2005, all new patients with symptoms of intermittent claudication referred to the Department of Vascular Surgery were considered for recruitment (Figure 1). Inclusion criteria were: 1) Symptoms of intermittent claudication (Rutherford category 1, 2, or 3) of at least 3 months duration; 2) a maximum pain-free walking distance of <350m; 3) an ankle-brachial index (ABI) of <0.9 at rest or a decrease in ABI after the treadmill test of >0.15; 4) one or more vascular stenoses of >50% diameter reduction or occlusions at the iliac or femoro-popliteal level; 5) informed consent. Exclusion criteria were: 1) presence of an abdominal aortic aneurysm; 2) life-incapacitating cardiac disease (NYHA classification II and higher[8]); 3) multilevel disease (i.e., stenoses/occlusions at both the iliac and femoral levels on the symptomatic side — multiple lesions limited to only the iliac or only the femoral level were not exclusion criteria); 4) isolated crural artery disease; 5) lesions deemed unsuitable for endovascular revascularization (iliac or femoropopliteal TASC-type D and some TASC type-B/C lesions[9]); 6) prior treatment for the same lesion (including exercise training). Multiple stenoses localized in one iliac arterial segment (i.e., common iliac or external iliac artery) were classified as a single lesion. Inclusion of the patient was decided at the multidisciplinary vascular conference by consensus between the vascular surgeons and interventional radiologists.

Figure 1: Flow diagram of study.

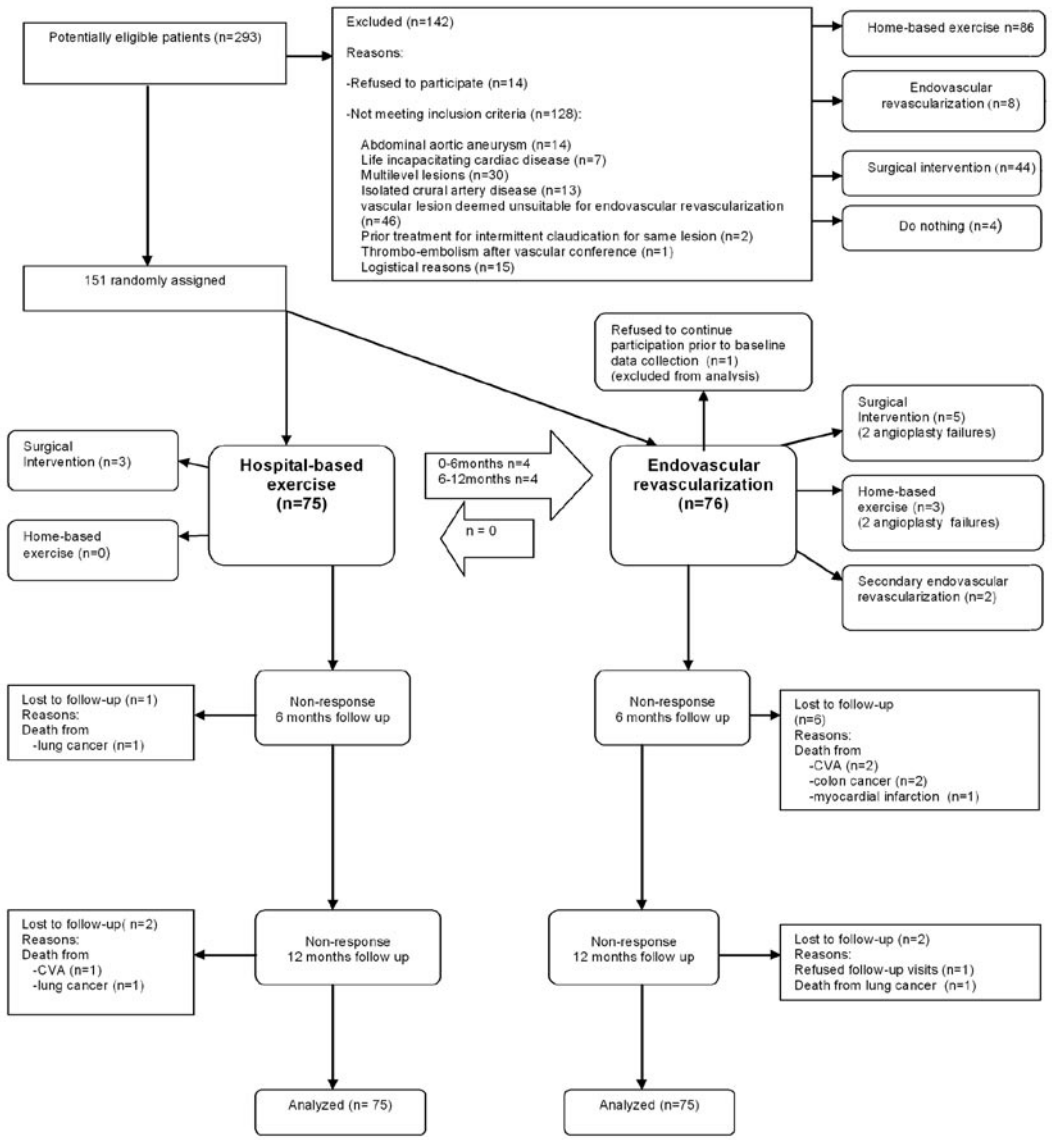


Diagram illustrates reasons for exclusion, random assignment to endovascular revascularization and supervised hospital-based exercise training and the treatment actually received, including 6- and 12-months follow-up.

After written informed consent was obtained, the patient was assigned to a specific treatment arm using a computer-generated randomization list that had been prepared in advance by an independent statistician. Block randomization with a block size of 16 was used. The local trial coordinator (SS) was unaware of treatment assignment prior to randomization.

INTERVENTIONS

Endovascular revascularization was performed as a balloon angioplasty-first approach followed by stent placement if the result of balloon angioplasty was deemed unsatisfactory. Revascularization was performed using a 10% oversized balloon (Powerflex or Opta-Pro; Cordis Johnson & Johnson; Miami, FL). For iliac revascularization, the initial balloon angioplasty was considered technically successful if the residual pressure gradient across the treated arterial segment was <10 mm Hg at rest. If the post-procedural pressure gradient exceeded 10mm Hg, a 9 mm-diameter, self-expanding nitinol stent was placed (Luminexx; Bard; Tempe AZ). In femoral revascularization, the decision to place an additional 6 mm-diameter self-expanding nitinol stent was based on evaluation of the post-balloon angioplasty angiogram.

Supervised hospital-based exercise was conducted on a walking treadmill for 30 minutes/session, twice weekly, during 24 weeks. A vascular technologist supervised each training session. Treadmill exercise was initiated at a workload of 3.5 km/h without a graded incline. Patients decreased workload to 1 km/h when, in their perception, maximum claudication pain occurred and continued exercising at this reduced workload until the pain subsided, usually after a brief period (range 1-3 minutes), after which the workload was increased again. If a patient improved his or her walking ability (as evidenced by an increase in maximum pain-free walking distance compared to previous sessions), the workload was increased by modifying the treadmill grade or speed (or both as tolerated) to ensure that there was always a stimulus of claudication pain during the workout. In addition, all patients were instructed to walk for at least 3x30 minutes weekly outside the hospital setting. After the 24-week supervised exercise program, patients were encouraged to continue their walking exercise in their own environment.

In addition to revascularization or exercise training, all patients underwent management of risk factors, including hypertension, serum glucose, cholesterol, lipid profile, and homocysteinaemia (in patients <50 years), and all were prescribed aspirin therapy (100 mg/day).

CLINICAL EFFECTIVENESS

Clinical effectiveness included clinical success, functional capacity, and health-related quality of life. Clinical success was defined as an improvement of at least one category in the Rutherford scale above the pre-treatment level, following the standards of the Society of Vascular Surgery/International Society of Cardiovascular Surgery (SVS/ISCVS).[10] Clinical success was measured one week after revascularization or after the first two exercise sessions (i.e., one week), and at 6 and 12 months of follow-up. Furthermore, we determined whether clinical success at follow-up was impaired by recurring symptoms of intermittent claudication on the initial symptomatic side (ipsilateral) or alternatively, by new symptoms on the contralateral side by using the presence of symptoms as a binary outcome (yes or no). We defined "contralateral symptoms" as the first occurrence of any contralateral symptoms in the limb including claudication and rest pain that was not the indication for the initial treatment.

Functional capacity was expressed as ABI, maximum pain-free walking distance, and maximum walking distance. The ABI was measured at rest and following treadmill walking (speed 3.5 km/h, without a graded incline) and the maximum- and pain-free walking distance were reported. Clinical success and functional capacity were both evaluated by an independent observer who was blinded to the specific treatment that had been assigned, and patients were instructed not to discuss their assigned treatment.

Health-related quality of life was assessed using the generic Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and the disease-specific Vascular Quality-of-life questionnaire (VascuQol).[11,12] The SF-36 was developed to evaluate physical-, social-, and physical-role functioning of patients and to elicit their perceptions of their general health and well-being in eight different health dimensions.[11] Based on a previous study, we determined that four of the eight health dimensions were relevant to describe the health status of intermittent claudication (physical-functioning, role-functioning limitations due to physical problems, bodily pain, and general health perceptions).[13] The scoring per dimension is valued on a 100-point scale from 0 (worst-outcome) to 100 (best-outcome). The VascuQol is a questionnaire especially developed for patients with peripheral arterial disease and is responsive to subtle effects after, for example, endovascular revascularization or exercise training.[12] The questionnaire contains five domains (activity, symptom, pain, emotion, and social functioning), in which 0 means death and 7 indicates maximum health.

In addition, the EuroQol-5D, rating scale, and costs were assessed, but these results are reported separately in a manuscript focusing on the cost-effectiveness outcomes.

DATA ANALYSIS

The required sample size was estimated based on the primary outcome, which was the mean improvement of quality-of-life. With adequate treatment, approximately 40-50% of patients were expected to have a substantial improvement of their symptoms after 6 months as measured by the physical functioning attribute of the SF-36.[13,14] A percentage difference of 20-25% between the treatment groups was considered to be clinically relevant.[15] To demonstrate a difference of 25% with an alpha of 0.05, a power of 0.80, and a 2-sided test of differences in unpaired proportions with an estimated 45% improvement in the control group, required 68 patients in each trial arm. With 2 trial arms, this implied recruiting 136 patients for the trial. To allow for some redundancy, we recruited 15 extra patients.

Results were analyzed according to the intention-to-treat principle, which implies that once a patient was randomly allocated, the patient remained in the allocated group for the analysis regardless of whether cross-over to the other strategy occurred and of whether follow-up was completed. The only patients excluded from the analysis were those for whom no data was available as they refused further participation immediately following randomization.

Significance of differences between group means at baseline was assessed with the unpaired t-test or the Mann-Whitney U-test, as appropriate, whereas dichotomous outcomes were assessed with the χ^2-test.

To assess the difference in the clinical success rate between the treatment groups, we calculated the Odds-Ratios (OR) of revascularization versus exercise at 6- and 12-months follow-up. To assess a possible interaction between the treatment strategy and the level of disease (iliac vs. femoral disease) on clinical success, we performed a logistic regression analysis. In the model, clinical success was the dependent variable, and an interaction term for treatment strategy and the level of disease was included. In addition, we calculated ORs to determine if the clinical success at follow-up became impaired by recurring symptoms of intermittent claudication on the initial symptomatic side or alternatively, by new symptoms on the contralateral side.

Significance of differences in mean score improvement between the treatment groups was assessed with the unpaired t-test or the χ^2-test. To adjust outcomes for imbalances of baseline values and characteristics between the treatment groups, we performed multivariable regression analysis. The variables included were baseline scores, age, gender, diabetes mellitus, smoking, hypertension, hyperlipidaemia, and disease severity (mild/moderate claudication vs. severe claudication). These variables were selected based on the TASC II report[3] and on clinical judgment. In the analyses, imputation of mean values for clinical success, functional capacity, and quality of life at 6- and 12-months follow-up was performed for patients who died of causes other than peripheral arterial disease and for patients who refused a follow-up visit.[16] There were no patients who died of peripheral arterial disease.

A significance level of 0.05 was considered statistically significant. Calculations were performed with SPSS 14.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Patients and treatments

During the inclusion period, 293 new, potentially-eligible patients with intermittent claudication were seen at the Department of Vascular Surgery (Figure 1). Fourteen patients refused to participate in the study, and 128 were excluded based on the study criteria. Thus, 151 patients entered the study, of whom 76 were randomized to revascularization and 75 to exercise training. One patient refused further participation after randomization to revascularization but before baseline data was collected. This patient was excluded from analysis. Thus, 150 patients were analyzed (Figure 1).

The two treatment groups had similar demographics and co-morbidities (Table 1). In addition, there was no significant difference at baseline in functional capacity or quality-of-life scores, except for the maximum pain-free walking distance, which was significantly higher in the exercise group ($p = 0.04$) (Table 1).

Table 2 shows the lesion characteristics of the two groups. Four patients failed endovascular revascularization technically. Two of these patients were advised a home-based exercise program, and 2 patients underwent surgery. Stents were used in 46 of 71 iliac lesions in 34 patients and in 20 of 40 femoral lesions in 16 patients. Asymptomatic iliac and femoral lesions on the contralateral side remained untreated. The two groups had a similar distribution of lesion characteristics (Table 2).

The mean number of sessions in the exercise program was 33 (+/-10; median 32). During follow-up, 10 patients in the revascularization group and 11 patients in the exercise group underwent additional treatment (Table 3). Eight patients in the exercise group underwent endovascular revascularization whereas no patient crossed-over in the opposite direction (Figure 1). There were 10 patients lost during the follow-up period because of death (n=9), or refusal to continue participation in the study at 12-months (n=1) (Figure 1). In the revascularization group, the response rate to the questionnaires was 92% (69 of 75) at 6 months and 89% (67 of 75) at 12 months. In the exercise group, the response rate was 99% (74 of 75) at 6 months, and 96% (72 of 75) at 12 months.

Clinical outcomes

Table 1: Baseline characteristics of patients and disease severity*

Characteristic	Endovascular revascularization(n=75) n (%)	Hospital-based exercise (n=75) n (%)	p-value
Age (y)	65 (+/- 11.4)	66 (+/- 9.1)	0.34
Male gender, %	44 (59)	39 (53)	0.62
Arterial hypertension† , %	32 (43)	28 (38)	0.87
Diabetes Mellitus, %	11 (16)	15 (24)	0.83
Hyperlipidemia‡, %	40 (53)	38 (51))	0.87
History of ischemic heart disease, %	14 (19)	21 (28)	0.19
Pulmonary disease, %	7 (9)	9 (12)	0.50
Osteo arthritis of the lower limb, %	7 (9)	5 (6)	0.66
Renal insufficiency, %	1(1)	3 (4)	0.35
History of cerebrovascular disease, %	8 (11)	4 (5)	0.32
Smoking, % current ever never	12 (16) 40 (53) 23 (31)	17 (23) 32 (43) 25 (34)	0.87
Body Mass Index	26 (+/-4.3)	25 (+/- 4.9)	0.88
Ankle-Brachial Index at rest § after exercise §	 0.62 (+/-0.18) 0.41 (+/-0.22)	 0.63 (+/-0.17) 0.42 (+/-0.21)	 0.62 0.60
Maximum pain-free walking distance (m)*	82 (+/- 48)	104 (+/- 65)	0.04
Maximum walking distance (m)	174 (+/- 76)	186 (+/- 97)	0.62
Rutherford classification¶, % 1 & 2 3	 57 (76) 18 (24)	 57 (76) 18 (24)	0.87
Quality of life SF-36 physical functioning " SF-36 role physical " SF-36 pain " SF-36 general health " VascuQol total**	 42 (+/-26) 37 (+/-52) 50 (+/-21) 53 (+/-23) 4.2 (+/-1.1)	 49 (+/-20) 49 (+/-45) 55 (+/-23) 54 (+/-20) 4.3 (+/-1.1)	 0.11 0.18 0.18 0.91 0.79

* Data are presented as mean (SD) unless otherwise indicated
† diastolic pressure > 95 mm Hg
‡ cholesterol ≥ 5.0 mmol/l
§ minimum of Right – Left
¶ Most severe classification per person
II SF-36 Dimension scores = 0-100 (worst-best) scale.
** VascuQol index scores = 1-7 (worst-best) scale

After revascularization the clinical success rate was 88% (66 of 75 patients; 95% CI 80, 96%) at 1-week, decreasing to 75% (56 of 75 patients; 95% CI 65, 85%) at 6 months and 68% (51 of 75 patients; 95% CI 57, 79%) at 12 months (Figure 2). After initiation of exercise, the clinical success rate was 16% (12 of 75 patients; 95% CI 8, 24%) at 1-week, increasing to a peak of 77% (58 of 75 patients; 95% CI 67, 87%) at 6 months and then decreasing to 65% (49 of 75 patients; 95% CI 54, 76%) at 12 months (the supervised exercise program lasted 6 months) (Figure 2). Although clinical success at 1 week was significantly higher with revascularization than with exercise (OR 39; 95% CI 15, 98, p<0.001), there was no statistically-significant difference at 6- or 12-months follow-up (75% vs. 77%; OR 0.9; 95% CI 0.4, 1.8, p=0.70 and 68% vs. 65%; OR 1.1; 95% CI 0.6, 2.2, p=0.73 respectively). Clinical success of revascularization versus exercise was not significantly associated with the interaction term "treatment group and level of disease" after 6- or 12-months (OR 2.1; 95% CI 0.9, 5.1, p=0.07 and OR 0.9; 95% CI 0.4, 1.8, p=0.70 respectively).

At 6 months after revascularization, there were significantly less patients with recurrent or remaining

Table 2: Baseline lesion characteristics

Variable	Endovascular revascularization (n=75) n (%)	Hospital-based exercise (n=75) n (%)	p-value
Iliac disease	55 (73)	51 (65)	0.47
Bilateral iliac disease	13 (17)	12 (16)	0.88
Unilateral both common and external iliac artery disease	3 (4)	5 (7)	0.77
	71	68	
Total number of iliac lesions	62(87)	61 (89)	0.90
Stenosis*	9 (13)	7(11)	0.96
Occlusion			
Femoral disease	20 (27)	24 (32)	0.47
Bilateral femoral disease	8 (11)	12 (16)	0.32
Unilateral multiple (>1) femoral lesions	5 (7)	6 (8)	0.17
Total number of femoral lesions	40	45	
Stenosis*	23 (58)	29 (64)	0.18
Occlusion	17 (42)	16 (36)	0.67

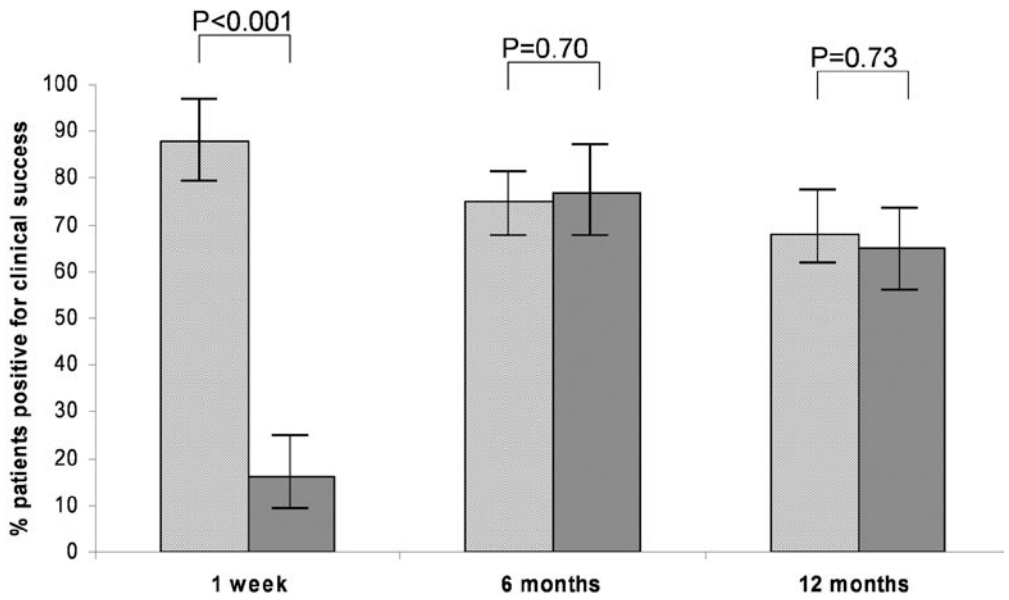
* Diameter reduction of 51-99%

symptoms of intermittent claudication on the ipsilateral side on the binary yes/no scale compared to the exercise group (37% vs. 69%; OR 0.4; 95% CI 0.2, 0.7, p<0.001) (Figure 3). However, there was no significant difference in symptoms on the ipsilateral side between the groups at 12 months (41% vs. 58%; OR 0.7; 95% CI 0.4, 1.3, p=0.25) (Figure 3). The percentage of patients with new symptoms of intermittent claudication on the contralateral side was higher — but not statistically-significant — in the revascularization group than in the exercise group after 6- and 12-months (17% vs. 8%; OR 2.4; 95% CI 0.9, 6.7, p= 0.09 and 21% vs.17%; OR 1.6; 95% CI 0.6, 4.2, p=0.34 respectively) (Figure 3).

After both revascularization and exercise, there was an improvement at both 6- and 12-months in the mean ABI, the maximum pain-free walking distance, and the maximum walking distance (Table 4). Prior to adjustment for baseline variables, the ABI improved more in the revascularization group, whereas the maximum pain-free walking distance and maximum walking distance improved more in the exercise group. After adjustment for baseline variables, only the difference in maximum pain-free walking distance at 6 months remained significant, being in favor of exercise (mean difference -16 meters; 95% CI -29, -2 meters, p=0.02).

After both revascularization and exercise, there was an improvement in both the mean quality-of-life

Figure 2. Clinical success at 1 week, 6- and 12-months after endovascular revascularization (light bars) or supervised hospital-based exercise (dark bars); Error bars indicate 95% confidence intervals.



scores of the SF-36 dimensions and the total score of the VascuQol (Table 5). Regardless of adjustment for the baseline variables, there were no significant differences in the quality-of-life scores between the two groups at 6- or 12-months follow-up (Table 5).

DISCUSSION

This prospective randomized controlled trial evaluated the effect of endovascular revascularization versus supervised hospital-based exercise training on clinical success, functional capacity, and quality of life after 6- and 12-months follow-up in patients with intermittent claudication. While patients receiving revascularization scored better for clinical success immediately after the start of treatment, the benefit over exercise was lost over time. Revascularization reduced ipsilateral symptoms at 6 months, but this did not translate into improved clinical success, functional capacity, or quality-of-life. There was a small but significant difference in favor of exercise in the maximum pain-free walking distance at 6 months. After 12 months, though, there were no significant differences between the treatment groups in functional capacity and the quality-of-life scores.

Before this trial there was no randomized controlled trial performed that evaluated clinical success, functional capacity, and quality of life after revascularization or exercise in patients with intermittent claudication. In a randomized controlled trial, which evaluated functional capacity, maximum walking distance at 6 years was better for patients treated with exercise training than for those treated with percutaneous transluminal angioplasty.[17] This study, however, was small and quality-of-life outcomes

Table 3: Additional treatment during follow-up

	Endovascular revascularization (n=75)		Supervised hospital-based exercise (n=75)	
Additional treatment	**0-6 months (n)**	**6-12 months (n)**	**0-6 months (n)**	**6-12 months (n)**
Home-based exercise	3	0	0	0
Endovascular revascularization with or without stent placement				
Common Iliac artery	0	1	2	3
Femoral artery	0	1	2	1
Surgical intervention				
Aorto-bifurcation graft	2	0	1	0
Femoral-femoral cross-over graft	1	0	0	0
Femoro-popliteal bypass	0	0	2	0
Patch plasty of common femoral artery	2	0	0	0

were not reported. A recently-published systematic review comparing effectiveness of exercise training and endovascular revascularization showed that quality of life was improved after both exercise training and endovascular revascularization at 6 months follow-up, whereas functional capacity improved only after endovascular revascularization.[14] This systematic review, however, was limited by the quality of the included studies. These were not randomized, had insufficient power, the data for quality of life and functional capacity were inconsistently reported, and the exercise training programs were not standardized.

Different exercise training studies have evaluated the efficacy of exercise programs, but the relative value of supervision is still controversial. Some studies, particularly in Europe, have shown good results from a home-based program;[18,19] however, other studies have shown little benefit from home-based exercise.[20] Supervised exercise, however, has provided consistent clinical improvement in almost every study.[20-23] Despite solid evidence that supervised exercise improves claudication distance and is better than a "go home and walk" advice, supervised exercise programs are not readily available, and many patients are unable or unwilling to participate. We experienced only minor resistance towards supervised exercise. Out of fourteen patients who refused participation in the trial, only four had an aversion to hospital-based exercise. As is reflected in the high compliance rate of our exercise group, most participants were retired and enjoyed the program.

From the patient's perspective, the most relevant outcome is probably the symptomatic outcome. We measured symptoms subjectively with a binary outcome (symptoms: yes-or-no), which may have been affected by the patient's attitude to his/her health status and care-giver. This could explain why more patients in the exercise group had ipsilateral symptoms at 6-months, despite the proportion of patients with clinical success being equal between the groups. Clinical success was based on the quantitative Rutherford criteria adopted by the SVS/ISCVS, including maximum walking distance and post-exercise ankle pressure.[24] These parameters are unlikely to be biased by attitude and are considered more objective.

Figure 3. Site of symptoms at 6- and 12-months after endovascular revascularization (light bars) or supervised hospital-based exercise (dark bars); Error bars indicate 95% confidence intervals.

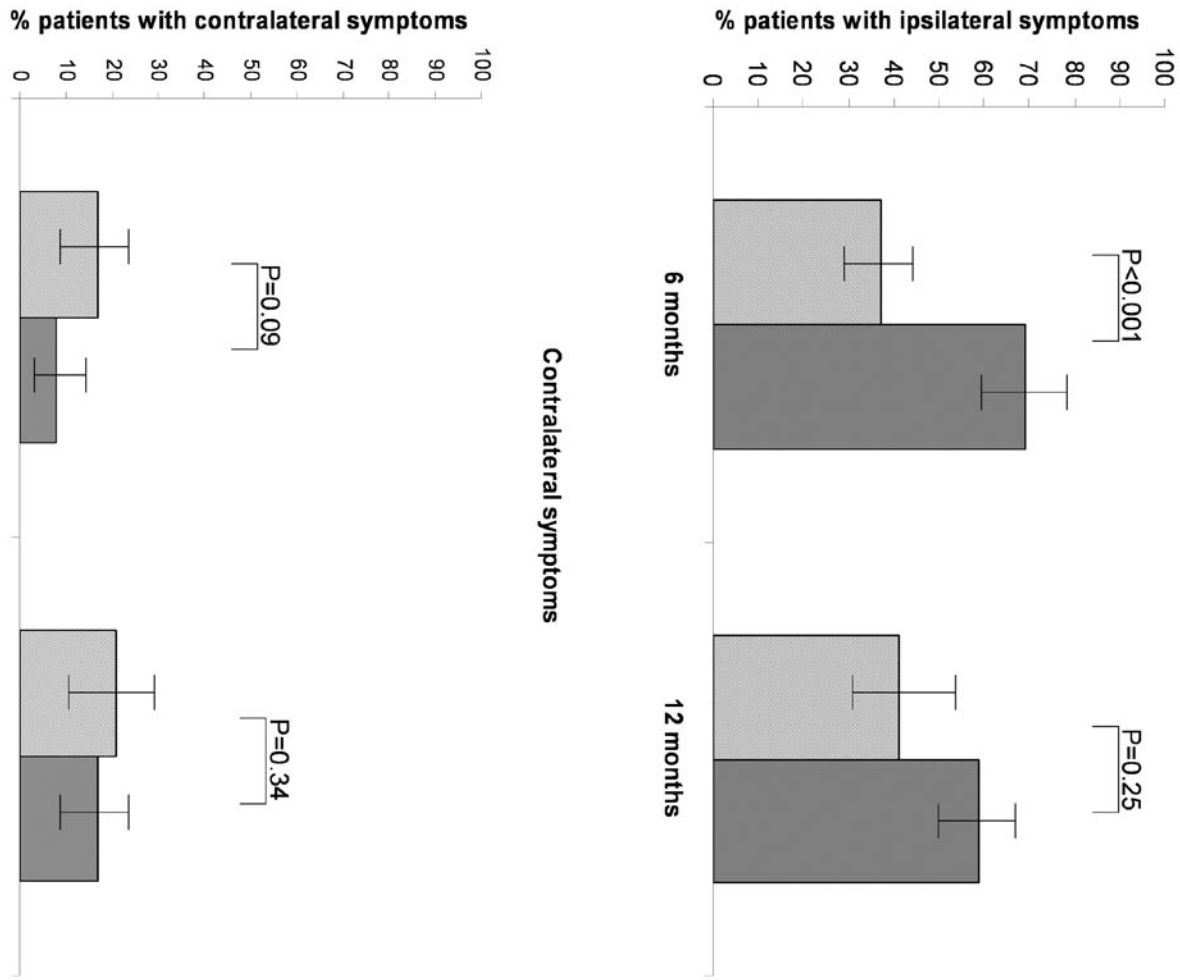


Table 4: Mean improvement in different measures of functional capacity during follow-up compared to baseline and differences between the groups (endovascular revascularization compared to hospital-based exercise*)

Measure of functional capacity	Mean score improvement (95% CI)				Unadjusted mean difference (95% CI)*		Adjusted mean difference (95% CI)*†		Adjusted p-value
	Endovascular revascularization (n=75)		Hospital-based exercise (n=75)						
ABI at rest 6 months ‡	0.14	(0.06, 0.18)	0.03	(-0.01, 0.06)	0.11	(0.04, 0.18)	0.00	(-0.04, 0.04)	0.92
ABI at rest 12 months‡	0.20	(0.10, 0.20)	0.04	(0.00, 0.07)	0.16	(0.06, 0.19)	0.00	(-0.03, 0.03)	0.97
Maximum pain-free walking distance 6 months (m)	679	(509, 819)	899	(740, 1042)	-220	(-445, 4)	-16	(-29, -2)	0.02
Maximum pain-free walking distance 12 months (m)	806	(638, 952)	943	(803, 1104)	-137	(-363, 88)	24	(-75, 26)	0.34
Maximum walking distance 6 months (m)	755	(616, 917)	1138	(1016, 1262)	-383	(-587, -178))	16	(-41, 74)	0.58
Maximum walking distance 12 months (m)	826	(669, 955)	1034	(909, 1171)	-208	(-411, -5)	24	(-26, 75)	0.34

Note:

Abbreviations: ABI = Ankle Brachial Index

* Positive difference indicates endovascular revascularization has a better outcome and negative number indicates supervised hospital-based exercise has a better outcome.

† Adjusted for baseline ABI, maximum pain-free walking distance, or maximum walking distance, age, sex, severity of disease (mild/moderate versus severe), smoking, hypertension, hyperlipidaemia, diabetes mellitus.

‡ Minimum of right-left

Table 5: Mean improvement in different measures of health-related quality of life during follow-up compared to baseline and differences between the groups (endovascular revascularization compared to hospital based exercise*)

Measure of quality of life	Mean score improvement (95% CI)				Unadjusted mean difference (95% CI) *		Adjusted mean difference (95% CI)*†		Adjusted p-value
	Endovascular revascularization (n=75)		Hospital-based exercise (n=75)						
SF-36-Physical functioning 6 months ‡	19	(14, 25)	12	(7, 18)	7	(-0.3, 15)	2	(-2, 6)	0.22
SF-36-Physical functioning 12 months	17	(12, 22)	13	(8, 18)	4	(-3, 12)	2	(-0.4, 5)	0.10
SF-36-Physical role functioning 6 months ‡	25	(14, 36)	14	(4, 24)	11	(-4, 27)	7	(-2, 16)	0.12
SF-36-Physical role functioning 12 months	21	(10, 32)	6	(-4, 16)	15	(-1, 30)	7	(-2, 16)	0.11
SF-36-Bodily pain 6 months ‡	14	(7, 21)	7	(2, 13)	7	(-1, 17)	4	(-1, 9)	0.11
SF-36-Bodily pain 12 months	11	(5, 17)	10	(4, 16)	2	(-7, 10)	3	(-1, 7)	0.20
SF-36-General health 6 months ‡	1	(-4, 6)	5	(1, 9)	-4	(-11, 2)	-1	(-5, 3)	0.74
SF-36-General health 12 months	2	(-3, 7)	5	(1, 9)	-3	(-9, 4)	-1	(-4, 3)	0.73
VascuQol 6 months §	0.6	(0.1, 1.1)	0.7	(0.4, 1.0)	-0.1	(-0.7, 0.6)	0.1	(-0.2, 0.4)	0.08
VascuQol 12 months	0.7	(0.3, 1.1)	0.6	(0.3, 0.9)	-0.1	(-0.4, 0.6)	0.1	(-0.1, 0.2)	0.61

Note:

* Positive difference indicates endovascular revascularization has a better outcome; negative number indicates supervised hospital-based exercise has a better outcome.

† Adjusted for baseline quality-of-life scores, age, sex, severity of disease (mild/moderate versus severe), smoking, hypertension, hyperlipidaemia, diabetes mellitus.

‡ SF-36 Dimension scores = 0-100 (worst-best) scale.

§ VascuQol iIndex scores = 1-7 (worst-best) scale

A previous meta-analysis concluded that after stent placement for aorto-iliac occlusive disease the long term failure was reduced compared to percutaneous transluminal angioplasty.[25] One of the limitations of our study was that endovascular revascularization was performed as a balloon angioplasty-first approach followed by stent placement if the result of balloon angioplasty was deemed unsatisfactory. The criterion for stent placement was a pressure gradient over the stenosis. Pressure gradient determination can be complex, and difficulties may have influenced the choice for stent placement, which in turn may have affected the outcome after endovascular revascularization, but this represents "real world clinical practice". One of the potential limitations of our study was that the results of endovascular revascularization, which reflected the clinical practice at the time of the study, may have been inferior to results achievable nowadays with better stents and different insights. For example, we now know that primary stent placement in the femoral arteries has better patency at 6- and 12-months than the balloon angioplasty-first approach followed here.[26,27] In addition, the specific stent type that we used in our practice has in a later study proved to be associated with lower patency than would be achievable with new generation stents combined with the use of clopidogrel (Plavix) after stent placement 27. Another limitation of our study is that bias towards exercise may have occurred in patients with bilateral symptoms, as walking inherently treats both limbs. The severity of ipsilateral symptoms at baseline may have disguised latent contralateral symptoms in some patients. After endovascular revascularization, increased mobility would encourage the discovery of the latent contralateral symptoms. However, most patients with bilateral lesions in the endovascular revascularization group were treated on both sides. Furthermore, peripheral arterial disease is a two-limb problem, so a patient-based treatment and analysis of the trial results is the appropriate approach.

In a previous randomized study, the combination of endovascular revascularization and home-based exercise gave better results than either intervention alone.[28] Unfortunately, this study included a relatively small number of patients. To the best of our knowledge, early intervention in addition to supervised exercise has never been studied in a large randomized controlled trial, but this combination could be an interesting treatment strategy. Endovascular revascularization followed by exercise training would presumably combine effective short-term relief of claudication symptoms with the added long-term benefits of exercise training. Patients may, however, be less motivated to exercise after the immediate benefit of the revascularization treatment. Furthermore, the cost-effectiveness of the combination would need to be evaluated.

In conclusion, our randomized controlled trial demonstrated that patients undergoing endovascular revascularization or supervised hospital-based exercise yielded similar benefit in clinical success, functional capacity, and quality-of-life after 6- and 12-months follow-up, whereas the benefit was more immediate with revascularization.

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5 COST-EFFECTIVENESS FOLLOWING TREATMENT OF INTERMITTENT CLAUDICATION: A RANDOMIZED CONTROLLED TRIAL

COST-EFFECTIVENESS OF ENDOVASCULAR REVASCULARIZATION COMPARED TO SUPERVISED HOSPITAL-BASED EXERCISE TRAINING IN PATIENTS WITH INTERMITTENT CLAUDICATION: A RANDOMIZED CONTROLLED TRIAL

ABSTRACT

Purpose: To compare the cost-effectiveness of endovascular revascularization versus supervised hospital-based exercise in patients with intermittent claudication during a 12-month follow-up period.

Materials and methods: Between September 2002-September 2005, we randomly assigned 151 consecutive patients with intermittent claudication, to receive either endovascular revascularization -angioplasty-first approach- ($n = 76$) or hospital-based supervised exercise ($n = 75$). The primary outcome was health-related quality of life using the EuroQol, rating scale, SF36 physical functioning, quality-adjusted life years (QALYs) accumulated over 12 months. Secondary outcomes were costs and incremental costs per QALY from the societal perspective. Significance of differences between the groups was assessed using the unpaired t-test, χ^2-test, or the Mann-Whitney U-test. We performed multivariable regression analysis to adjust outcomes for imbalances of baseline values.

Results: The endovascular revascularization group had a larger improvement in 6- and 12-months EuroQol, rating scale, and SF36 quality-of-life values than the supervised hospital-based exercise, but the differences were not statistically significant. The gain in total mean QALYs accumulated during 12 months, adjusted for baseline values, was significantly larger following endovascular revascularization (mean difference 0.03; 95% CI: 0.02, 0.04; $p < 0.001$). The total mean cumulative costs per patient were significantly higher in the endovascular revascularization group (mean difference €2318; 95% CI: €2176, €2460; $p < 0.001$) and the incremental cost per QALY was €77 267.

Conclusion: Endovascular revascularization results in a small gain in effectiveness compared to supervised hospital-based exercise during 12-months follow-up but costs more, and only if society is willing-to-pay more than 77 300 €/QALY gained should one consider endovascular revascularization as first-line treatment in patients with intermittent claudication.

INTRODUCTION

Intermittent claudication is the mildest manifestation (i.e., Rutherford category 1, 2 or 3) of peripheral arterial disease, with a prevalence around 5% in men older than 50 years.[1,2] As the incidence of intermittent claudication will increase over the next decades due to the aging population in Western societies, the economic impact of intermittent claudication is expected to be substantial.[3]

The treatment goal for intermittent claudication is to improve health-related quality of life. The general consensus is to initially treat with exercise training, but endovascular revascularization is increasingly performed because of its technical innovations, immediate success, and low risks of peri-procedural mortality and morbidity.[4] In addition to effectiveness, however, one needs to consider costs and cost-effectiveness. Initial hospital costs for endovascular revascularization are likely higher than those for exercise training. Besides these initial hospital costs, costs of follow-up are important to take into account, such as the costs of diagnostic tests for recurrent symptoms and secondary treatment.

The present study compared endovascular revascularization versus supervised exercise training as first-line treatment of intermittent claudication, with regard to cost-effectiveness during 12-month follow-up in a prospective randomized controlled trial.

METHODS

Study design and patients

The study was a randomized controlled clinical trial comparing endovascular revascularization to supervised hospital-based exercise in patients with symptoms of intermittent claudication (Rutherford category 1, 2, or 3). The study was performed following Good Clinical Practice and was registered (ISRCTN 64443682).[5] Data were analyzed and reported according to CONSORT guidelines.[6] Institutional Review Board approval was obtained and all patients gave written informed consent.

All patients referred to the Department of Vascular Surgery with intermittent claudication from September 2002–September 2005 were considered for recruitment (Figure 1). Inclusion criteria were: 1) Symptoms of intermittent claudication (Rutherford category 1, 2, or 3) of at least 3 months duration; 2) a maximum pain-free walking distance of <350 m during a treadmill test; 3) an ankle-brachial index (ABI) of <0.9 at rest or a decrease in ABI after the treadmill test of >0.15; 4) one or more vascular stenoses of >50% diameter reduction or occlusions at the iliac or femoro-popliteal level; 5) written informed consent. Exclusion criteria were: 1) presence of an abdominal aortic aneurysm; 2) life-incapacitating cardiac disease (NYHA classification II and higher[7]); 3) multilevel disease (i.e., stenoses/occlusions at both the iliac and femoral levels on the symptomatic side — multiple lesions limited to only the iliac or only the femoral level were not exclusion criteria); 4) isolated crural artery disease; 5) lesions deemed unsuitable for endovascular revascularization (iliac or femoropopliteal TASC-type D and some TASC type-B/C lesions;[8] 6) prior treatment for the same lesion (including exercise training).

After all diagnostic tests had been performed, indication for treatment and in- and exclusion criteria were assessed at the vascular conference by consensus between the vascular surgeons and interventional radiologists. An independent statistician prepared a computer-generated randomization list with a block size of 16. Study personnel dealing with bias-sensitive data were blinded to the assigned treatment and block size.

Figure 1: Flow diagram of study.

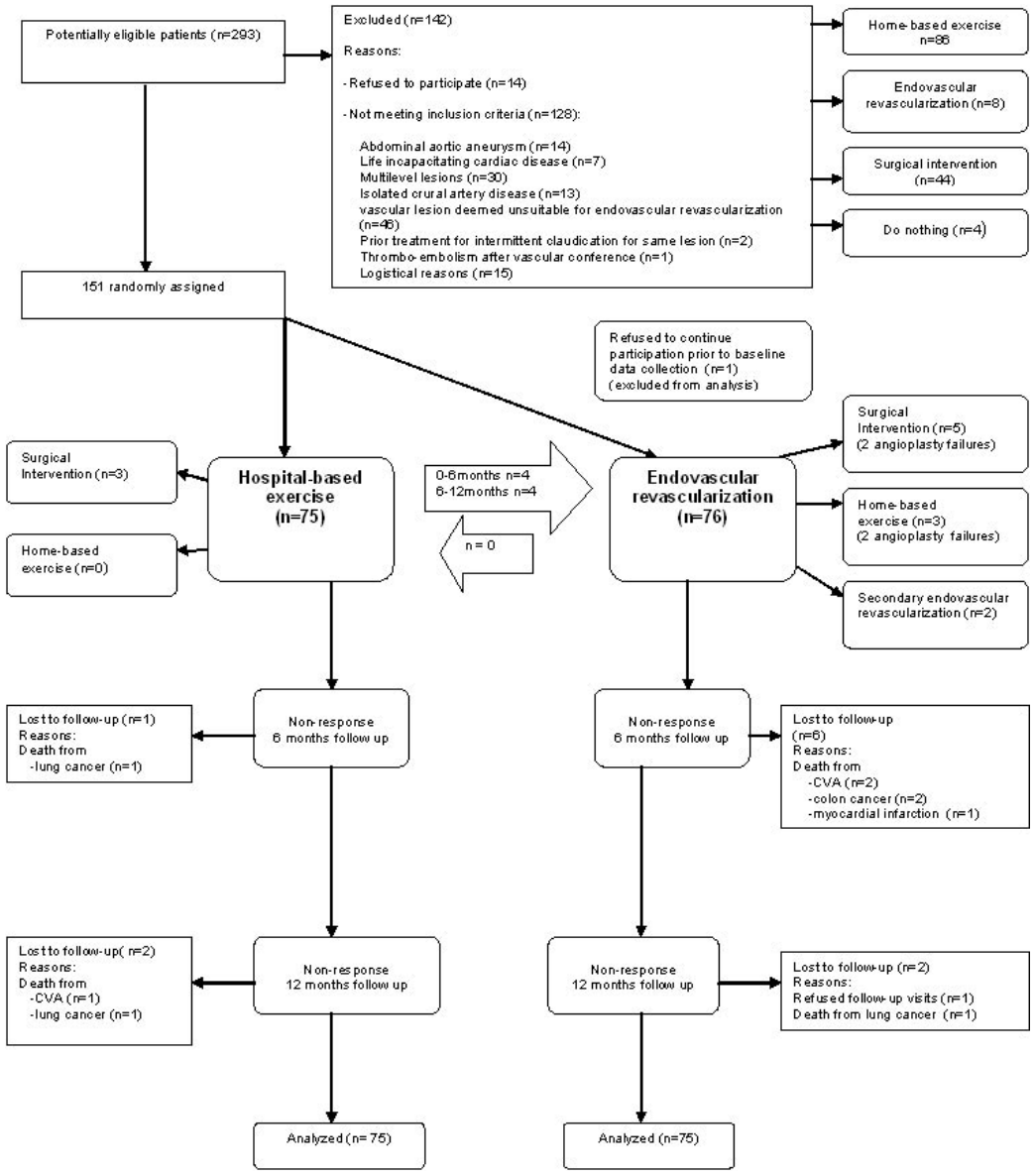

Diagram illustrates reasons for exclusion, random assignment to endovascular revascularization and supervised hospital-based exercise training and the treatment actually received, including 6- and 12-months follow-up.

Procedures

Endovascular revascularization was performed using a 10% oversized balloon (Powerflex or Opta-Pro; Cordis Johnson & Johnson; Miami, FL). For iliac revascularization, the initial balloon angioplasty was considered technically successful if the pressure gradient across the treated arterial segment was <10 mm Hg at rest. If balloon dilatation was inadequate, a 9 mm diameter self-expanding nitinol stent (Luminexx; Bard; Tempe, AZ) was placed during the same session. For femoral revascularization, the decision to place an additional 6mm diameter self-expanding nitinol stent was based on evaluation of the post-balloon angioplasty angiogram.

Treadmill exercise was conducted in the hospital twice weekly over a 24-week period, supervised by a vascular technologist. Each session began at 3.5 km/h without incline, and workload was increased (speed or incline as tolerated) until a severe level of claudication pain was reached. The workload was lowered to 1 km/h until the pain abated and the patient resumed walking at higher workload. This process was repeated for 30 minutes. In addition, all patients were instructed to walk at home for at least 3x30 minutes weekly. Feedback and evaluation of these home-based exercise hours were also reported. After the 24-week period, patients were advised to continue exercise at home.

Before randomization, all patients underwent management of risk-factors, including hypertension, serum glucose, cholesterol, lipid profile, and homocysteinaemia (if age <50 years), and all were prescribed aspirin therapy (100 mg/day).

Outcomes

The outcomes of interest were effectiveness expressed as mean improvement of health-related quality of life over the 12-month period and cumulative 12-month costs. Quality of life was assessed using a self-administered questionnaire. Costs were assessed from the societal perspective, according to national guidelines for cost-analyses.[9] Functional capacity and clinical success were also assessed but are reported separately in a manuscript focusing on the clinical outcomes.

The questionnaire consisted of the EuroQol-5D (EQ-5D), rating scale, and the dimension "physical functioning" of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). The EQ-5D is a multi-attribute utility instrument that assesses quality-of-life values from the societal perspective and classifies patients into a health-state.[10] For each health-state, a value was calculated using the Dutch scoring algorithm, which was derived from the general population:[11] 0 equates to death and 1 equates to maximum health.

The rating scale required the respondent to rate their overall health on a scale from 0-100, where 0 represents death and 100 perfect health.[12] The SF-36 was developed to evaluate physical, social, and physical-role functioning of patients, and it elicits their perceptions of their general health and well-being in eight different health dimensions.[13] "Physical functioning" is most relevant to peripheral arterial disease, and we restricted this analysis to it.[14] The SF-36 was valued on a 100-point scale: 0 means death and 100 indicated maximum health.

Quality-adjusted life years (QALYs) accumulated during the 12-month follow-up period were based on the EQ-5D values at baseline, 6-months, and 12-months.

Costs (medical and non-medical) of all relevant items used during the entire trial were collected. Direct medical costs included costs of all therapeutic procedures, personnel, materials, equipment, additional associated diagnostic or therapeutic procedures, and associated hospital admissions during 12-months follow-up. Personnel costs were computed by multiplying time spent with the mean wage rate of the appropriate personnel-category and adding 37% social-security.[9] Costs of materials were summed cost prices. Equipment costs were calculated as: [time spent on a procedure] * [hourly cost]. The annuitized hourly costs of equipment were summed with servicing costs and divided by

the proportion of total available room time (33% of a 40-hour work-week for endovascular revascularization and 80% of a 40-hour work-week for supervised exercise).[9]

Non-direct medical costs included costs of supporting departments, housing, overhead, transportation costs, and patient time costs. The costs of supporting departments were obtained from records of our financial department; housing and overhead were estimated at 45% of direct assignable costs.[9] Transportation costs included parking costs and mean estimated gasoline costs. Patient-time costs were [hourly wage rate] * [number of hours in-hospital]. The hourly wage rate was estimated with the published mean hourly wage rate for Dutch men and women given for different age categories (25-44, 45-54, 55-64, >65). The time required for treatment was based on the length of hospitalization, which was estimated from the records of patients undergoing revascularization (8 hours) and/or the exercise program (30min*number of sessions). In addition, time invested in unsupervised exercise at home was reported and included in the patient-time cost analysis.

Costs were discounted at a rate of 3% per annum.[15] All costs are reported in 2005 euros using the consumer price indices of the Central Bureau of Statistics, the Netherlands.[16, 17]

Data analysis

With adequate treatment, 40-50% of patients were expected to have a substantial improvement of their symptoms after 6 months as measured by the dimension "physical functioning" on the SF-36.[14, 18] A percentage difference of 20-25% between the treatment groups was considered clinically relevant.[19] With these assumptions, 68 patients were required in each trial arm for a power of 80% and a 5% significance level. Anticipating a 5-10% loss to follow-up, we recruited 15 extra patients.

Results were analyzed according to the intention-to-treat principle: we analyzed all patients according to their allocated intervention irrespective of cross-over to the other strategy or completion of follow-up. The only patients excluded from the analysis were those for whom no data was available as they refused further participation immediately following randomization. In addition, results were analyzed with imputation of mean values for quality of life at 6- and 12-months follow-up for patients who died of causes other than peripheral arterial disease and for patients who refused a follow-up visit.[20] There were no patients who died of peripheral arterial disease, and there were no missing cost values. To calculate 95% confidence intervals of the mean cost values and of the mean cost differences, we used the bootstrap resample method.[21]

QALY improvement accumulated during the 12-month follow-up period was calculated per patient as the integral under the EQ-5D graph as a function of time adjusted for the baseline value. In the revascularization group we assumed that the EQ-5D graph increased immediately after the last intervention to the 6-month value, whereas in the exercise group we interpolated between the baseline value and the 6-month value to account for the gradual improvement during the course of the 24-week training program. In addition, we calculated the incremental cost-effectiveness ratio (ICER) as the difference in mean cumulative total costs divided by the difference in mean QALY improvements accumulated during 12 months for the revascularization group compared to the exercise group.

To adjust outcomes for potential imbalances of baseline values and characteristics between the treatment groups, we performed multivariable regression analyses. The variables included in the multivariable regression analyses were baseline quality-of-life scores, age, gender, diabetes mellitus, smoking, hypertension, hyperlipidaemia, and disease severity (mild/moderate claudication vs. severe claudication). The variables were selected based on the TASC-II report and on clinical judgment.[22]

Significance of differences between group means was assessed with the unpaired t-test or the Mann-Whitney U-test, as appropriate, whereas significance of dichotomous outcomes was assessed with the χ^2-test. For the analyses, a significance level of 0.05 was used. Calculations were performed with SPSS 14.0 for Windows (SPSS Inc., Chicago, IL), and R version 2.5 (R Foundation, Vienna, Austria).

RESULTS

Patients

Figure 1 shows the flow diagram of patients entering the randomized controlled trial, including the actual treatments received and patients who were lost to follow-up. One patient, who refused further participation before baseline data was collected, was excluded from the analysis. Thus, 150 patients were analyzed for quality-of-life and costs (Figure 1). In the revascularization group, four patients technically failed initial treatment. Two were advised home-based exercise, and two underwent surgical intervention (Figure 1).

Demographics, co-morbidities, baseline Rutherford classification, ABI at rest and after exercise, maximum walking distance, and quality-of-life scores did not differ between the groups (Table 1), except for the maximum pain-free walking distance at baseline. This was significantly lower in the revascularization group compared to the exercise group (p=0.04).

During follow-up, the response rate to the questionnaires in the revascularization group was 92% (69 of 75 patients) at 6 months and 89% (67 of 75 patients) at 12 months. In the exercise group, the response rate was 99% (74 of 75 patients) at 6 months and 96% (72 of 75 patients) at 12 months.

Outcomes

After both revascularization and exercise, all quality-of-life questionnaires showed a significant improvement at 6- and 12-months compared to pre-treatment values (Table 2). The treatment groups differed slightly – albeit not significantly – in the EuroQol, rating scale, and SF36 values in favor of the revascularization group at 6- and 12-months, with or without adjustment for baseline variables. The exception to this was the rating scale score at 12 months, which was higher (but not significant) in the exercise group without adjustment. The QALY improvement accumulated during 12-months follow-up was significantly more in the revascularisation group than in the exercise group (mean difference 0.08; CI 0.03, 0.12; p=0.01) (Table 2). After adjustment for baseline variables this difference was smaller but still significant (mean difference 0.03;CI 0.02, 0.04; p<0.001) (Table 2).
The total mean cumulative costs per patient during 12 months were €4254 higher in the revascularization group than in the exercise group (95% CI €1648, €7734; p< 0.001) (Table 3). Adjustment for baseline variables reduced this difference somewhat (mean difference €2318; 95% CI €2176, €2460; p<0.001) (Table 3).

Although personnel costs were similar, all other procedure costs were significantly higher for revascularization than for exercise (Table 3). Patient costs in the revascularization group were lower than those in the exercise group (mean difference €539; 95% CI €444, €636; p<0.001). This was due to the time investment in the exercise program. Total mean follow-up costs in the revascularization group were higher than in the exercise group (mean difference €2422; 95% CI -€219, €6072; p=0.15), but

Table 1: Baseline characteristics of the study participants*

	Endovascular revascularization (n=75)	Hospital-based exercise (n=75)	p-value
Age (y)	65 (+/- 11)	66 (+/- 9)	0.34
Male gender, %	44 (59)	39 (53)	0.62
Arterial hypertension, %	32 (43)	28 (38)	0.87
Diabetes Mellitus, %	11 (16)	15 (24)	0.83
Hyperlipidaemia, %	40 (53)	38 (51))	0.87
History of ischemic heart disease, %	14 (19)	21 (28)	0.19
Pulmonary disease, %	7 (9)	9 (12)	0.50
Osteo arthritis of the lower limb, %	7 (9)	5 (6)	0.66
Renal insufficiency, %	1(1)	3 (4)	0.35
History of cerebrovascular disease, %	8 (11)	4 (5)	0.32
Smoking, % current ever never	12 (16) 40 (53) 23 (31)	17 (23) 32 (43) 25 (34)	0.87
Body Mass Index	26 (+/- 4)	25 (+/- 5)	0.88
Ankle-Brachial Index† at rest after exercise	 0.62 (+/-0.18) 0.41 (+/-0.22)	 0.63 (+/-0.17) 0.42 (+/-0.21)	 0.62 0.60
Pain-free walking distance (m)	82 (+/- 48)	104 (+/- 65)	0.04
Maximum walking distance (m)	174 (+/- 76)	186 (+/- 97)	0.62
Rutherford classification‡ , % 1 & 2 3	 57 (76) 18 (24)	 57 (76) 18 (24)	0.87
Quality of life EuroQol-5D § Rating scale ‖ SF-36 Physical functioning¶	 0.66 (+/- 0.20) 62 (+/- 17) 42 (+/- 26)	 0.69 (+/- 0.21) 65 (+/- 18) 49 (+/- 20)	 0.22 0.47 0.11

* Mean +/- SD in parentheses, unless otherwise indicated. † Minimum of Right – Left. ‡ Most severe classification per person. § EuroQol-5D with Dutch algorithm was used; EuroQol-5D value= 0-1 (death -maximum health) scale. ‖ rating scale= 0-100 (worst-best) scale. ¶ SF-36 Dimension scores = 0-100 (worst-best) scale.

were only significantly different for the outpatient visits (Table 3). After adjustment, the difference was significant. As the revascularisation group needed more surgical interventions during follow-up (5 vs 3 in the exercise group), additional admission costs were higher (Table 3).

Table 2: Mean improvement in quality of life compared to baseline and differences between the groups (endovascular revascularization compared to supervised hospital-based exercise *)

	Mean score improvement (95% CI) *				Unadjusted mean difference (95% CI) *		Adjusted mean difference (95% CI) *†		Adjusted p-value
	Endovascular revascularization (n=75)		Hospital-based exercise (n=75)						
EQ-5D 6 months‡ EQ-5D 12 months	0.16 0.1i	(0.10, 0.21) (0.04, 0.18)	0.09 0.07	(0.03, 0.15) (0.02, 0.13)	0.07 0.04	(-0.02, 0.15) (-0.06, 0.15)	0.02 0.02	(-0.05, 0.08) (-0.06, 0.09)	0.59 0.63
Rating scale 6 months ‖ Rating scale 12 months	8 4	(5, 12) (0, 9)	5 6	(1, 9) (2, 11)	3 -1	(-2, 9) (-8, 4)	1 1	(-3, 5) (-2, 4)	0.74 0.60
SF-36-Physical functioning 6 months ‖ SF-36-Physical functioning 12 months	19 17	(14, 25) (12, 22)	12 13	(7, 18) (8, 18)	7 4	(-0.3, 15) (-3, 12)	2 2	(-2, 6) (-0.4, 5)	0.22 0.10
Quality-adjusted life years accumulated during 12 months	0.14	(0.11, 0.18)	0.06	(0.04, 0.09)	0.08	(0.03, 0.12)	0.03	(0.02, 0.04)	<0.001

* Positive difference indicates endovascular revascularization has a better outcome; negative number indicates supervised hospital-based exercise has a better outcome. † Adjusted for baseline quality-of-life scores, age, sex, severity of disease (mild/moderate versus severe), smoking, hypertension, hyperlipidaemia, and diabetes mellitus. ‡ EuroQol-5D with Dutch algorithm was used; EuroQol-5D value= 0-1 (death -maximum health) scale. ‖ Rating scale and SF-36 Dimension scores = 0-100 (worst-best) scale.

The data above shows that revascularization is significantly more effective than exercise, but it is also more expensive. The incremental cost-effectiveness ratios were 53 175 €/QALY without adjustment and 77 267 €/QALY with baseline-variable adjustment (Table 4).

DISCUSSION

In this prospective randomized controlled trial, the cost-effectiveness of endovascular revascularization was compared to that of supervised hospital-based exercise in patients with intermittent claudication after 12-months follow-up. The results showed that quality of life improved after both treatments. There was a non-significant difference in the 6- and 12-month EuroQol, rating scale, and SF36 quality-of-life values between the treatment groups in favor of revascularization. The QALYs accumulated during 12 months were significantly higher after endovascular revascularization but revascularization was also significantly more expensive than supervised hospital-based exercise. Furthermore, the incremental costs/QALY gained by revascularization compared to exercise were higher than the generally-accepted willingness-to-pay threshold of 50 000 €/QALY and revascularization can only be considered cost-effective if society is willing-to-pay at least 77 300 € per QALY gained.

Prior to the current randomized controlled trial, there was no level-I evidence with respect to the effectiveness and costs of treatment for intermittent claudication. In the published literature about intermittent claudication, one previous study compared quality of life and costs for percutaneous transluminal angioplasty, bypass surgery, or exercise using a Markov decision analysis and data from cohort studies.[23] This study showed that quality-adjusted life expectancy was higher after vascular interventions than after exercise, with incremental cost-effectiveness ratios of 38 000 $/QALY gained when angioplasty was performed whenever feasible versus exercise alone and $311 000 allowing for additional bypass surgery, if necessary. In our study vascular intervention consisted primarily of percutaneous intervention — bypass surgery was used in only a few cases. We found an incremental cost-effectiveness ratio of nearly 80 000 €/QALY (in dollars approximately 110 000 $/QALY) which is consistent with previously published results.

Table 3: Total mean cumulative costs per patient during 12 months of follow-up after endovascular revascularization and supervised hospital-based exercise

	Endovascular revascularization (n=75)	Hospital-based Exercise (n=75)	Unadjusted meandifference (95% CI)	Adjusted mean difference (95% CI) *	Adjusted p-value
Procedure Material costs	€ 1444	€ 1			
Personnel costs	€ 441	€ 433			
Equipment costs	€ 76	€ 51			
Associated admission costs	€ 217	€ 0			
Total mean cumulative procedure costs	€ 2178 (1949, 2419)	€ 485 (454, 515)	€ 1692 (1454, 1938)	€ 1035 (903, 1167)	<0.001
Patient Transportation costs	€ 13	€ 164			
Productivity losses	€ 552	€ 941			
Total mean cumulative patient costs	€ 565 (519, 612)	€ 1104 (1021, 1189)	€ 539 (444, 636)	€ 504 (463, 546)	<0.001
Follow-up Associated outpatient visits and ABI measurements	€ 86	€ 0			
Additional imaging costs	€ 65	€ 92			
Additional therapeutic costs	€ 657	€ 532			
Additional admission costs†	€ 2578	€ 339			
Total mean cumulative follow-up costs	€ 3401 (865, 7018)	€ 958 (333, 1769)	€ 2422 (-219, 6072)	€205 (187, 223)	<0.001
Total mean cumulative housing/ supporting departments/overhead costs	€ 793 (767, 818)	€ 207 (203, 211)	€ 586 (561, 611)	€ 586 (560, 611)	<0.001
Total mean cumulative costs	€ 7031 (4522, 10556)	€ 2771 (2158, 3591)	€ 4254 (1648, 7734)	€ 2318 (2176, 2460)	<0.001

ABI = Ankle Brachial Index, 95% CI = 95% confidence interval determined with the bootstrap resample method.
* Adjusted for age, sex, severity of disease (mild/moderate versus severe), smoking, hypertension, hyperlipidaemia, and diabetes mellitus.
† In the endovascular revascularization group, the additional admission costs were due to surgical interventions (n=5) and secondary endovascular revascularizations (n=2). In the supervised hospital-based exercise group, the additional admission costs were due to surgical interventions (n=3) and endovascular revascularizations (n=8).

Even though the incremental effects gained in our results were in favor of revascularization for the treatment of intermittent claudication, exercise has some advantages as well. Exercise increases the functional capacity and decreases intermittent claudication symptoms by several mechanisms, including improvements in endothelial vasodilator function, skeletal-muscle metabolism, blood viscosity, and inflammatory responses,[24] but this means that mobility only improves slowly. A disadvantage is the required time investment on the part of the patient. After endovascular revascularization, there is immediate improvement in mobility, and only one post-interventional outpatient visit is required. Note that the time investment on the part of the patient was accounted for in our analysis by considering patient time costs.

Individual aspects should also play a role in the choice of primary treatment. For patients who are unable to perform their normal work or other activities important to them, endovascular revascularisation may be preferable to an exercise program. Also, the motivation of the patient to participate in an exercise program could play a role in the choice and success of treatment. Endovascular revascularization, however, has higher initial costs. Besides the higher initial costs, we also found higher

Table 4: Unadjusted and adjusted difference in mean cumulative total costs, mean QALY improvement, and incremental cost-effectiveness ratios per patient during 12 months of follow-up after endovascular revascularization and supervised hospital-based exercise

	Unadjusted *	Adjusted *†
Difference in cumulative mean total costs	€4254 (1648, 7734)	€2318 (2176, 2460)
Difference in QALY improvement accumulated during 12 months	0.08 (0.03, 0.12)	0.03 (0.02, 0.04)
Incremental cost-effectiveness ratio*	53 175 €/QALY	77 267 €/QALY

QALY = quality-adjusted life year.
* Endovascular revascularization compared to hospital-based exercise.
† Adjusted for baseline EuroQol, age, sex, severity of disease (mild/moderate versus severe), smoking, hypertension, hyperlipidaemia, and diabetes mellitus.

follow-up costs as revascularization patients had more surgical interventions than exercise patients, who tended to get a (less-expensive[25]) endovascular revascularization if secondary treatment was needed. This difference in secondary treatment arose because three arterial lesions were not suitable for endovascular (re-)intervention after prior failure and because of surgeon preference in two patients. Whatever the treatment considered, if the initial procedure failed, total costs during 12-month follow-up are 2- to 4-fold higher than if the initial procedure was successful.[22, 26]

Our study may have lacked power as it was designed to visualise clinically-relevant differences, rather than equivalences, in quality of life. Although the differences in the 6- and 12-month quality-of-life results were small and non-significant, we did find a significant difference in the QALY improvement accumulated during 12-months follow-up. Furthermore, it should be noted that quality of life is a subjective outcome which may be influenced by the perception of individual subjects. Patients in the exercise group may have underestimated their quality of life since improvement in symptoms occurs slowly during an exercise program and may therefore have been less noticeable. Conversely, the revascularization group may have overestimated their quality of life since their improvement after treatment was immediate and therefore would have contrasted with the pre-intervention state. This may indicate that the difference in quality of life between the treatment groups may in fact have been in favor of exercise. Furthermore, we had limited follow-up time-points and for revascularization we assumed that the EQ-5D value immediately after the last intervention equaled that of the first measured value, which was at 6 months, whereas the values with exercise gradually increased during the course of the 24-week training program. Another limitation could be that our study took place in a single centre and with adherence to strict in- and exclusion criteria, which may affect whether these results may be generalised. The advantage of our single centre study and adhering to strict in- and exclusion criteria is the homogeneous group of study participants, as illustrated by the baseline characteristics.

As with every randomized trial, we could only evaluate a limited number of strategies. In addition to revascularization and exercise training, other treatment strategies are of interest, for example, optimal medical treatment in combination with home-based exercise or optimal medical treatment combined with percutaneous transluminal angioplasty, which have been compared in a previous randomized study.[27] Other interesting treatment arms could be revascularization plus supervised exercise training or revascularization plus pharmacologic therapy. Indeed, regardless of the initial treat-

ment, claudicants should be encouraged to engage in regular exercise, and atherosclerotic risk factors need ongoing attention during the follow-up period.

In conclusion, endovascular revascularization results in a small gain in effectiveness compared to supervised hospital-based exercise during 12-months follow-up but costs more, and only if society is willing-to-pay more than 77 300 €/QALY gained should one consider endovascular revascularization as first-line treatment in patients with intermittent claudication.

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6 PRESENCE AND INFLUENCE OF PERIPHERAL ARTERIAL DISEASE ON THE CLINICAL EFFECTIVENESS OF CARDIAC REHABILITATION

PRESENCE AND INFLUENCE OF PERIPHERAL ARTERIAL DISEASE ON THE CLINICAL EFFECTIVENESS OF CARDIAC REHABILITATION

ABSTRACT

Purpose: To evaluate whether clinical effectiveness of cardiac rehabilitation is related to the presence of peripheral arterial disease (PAD).

Materials and methods: From a consecutive cohort of patients who started cardiac rehabilitation from January 2004 to December 2004, we included those who completed the Walking Impairment Questionnaire (WIQ) (n=126). Cardiac rehabilitation failure was defined as a premature discontinuation of the treadmill exercise program or an inability to reach target heart rate. Presence of PAD was based on the walking distance score and the speed score of the WIQ and in a subset of our patient sample (n=39) we assessed the ABI. Chi-squared tests were used to compare the proportion of patients with PAD between patients who failed cardiac rehabilitation and patients who were successful. In addition, age and sex adjusted logistic regression models were used to examine the association between cardiac rehabilitation failure and the presence of PAD.

Results: The presence of PAD based on the walking distance score of the WIQ was significantly higher in the cardiac rehabilitation failure group than in the success group (34% vs.17%, OR 2.5; 95% CI 1.1 to 6.0, p=0.03), whereas the presence of PAD based on the walking speed score was not significantly different (30% vs. 28%, OR 1.1; 95% CI 0.5 to 2.5, p=0.79). The presence of PAD based on ABI measurements was higher in the failure group than in the success group (39% vs.14%, OR 3.8; 95% CI 0.8 to 17.9, p=0.08). Logistic regression analysis showed that when cardiac rehabilitation failure was adjusted for age and sex, failure was significantly associated with the presence of PAD based on the walking distance (OR 2.8; 95% CI 1.1 to 7.1, p=0.03), but not significantly associated when based on the speed score (OR 1.2; 95% CI 0.5 to 2.8, p=0.72).

Conclusion: This study demonstrated that the clinical effectiveness of cardiac rehabilitation was inversely related to the presence of PAD, which suggests that patients with PAD benefit less from a cardiac rehabilitation program and are at higher risk of future cardiac events.

BACKGROUND

Coronary artery disease (CAD) is the main cause of death in the United States.[1] Millions of Americans have a history of myocardial infarction (MI) or experience angina pectoris.[1] Risk factors of CAD do not differ from those of atherosclerotic disease in other circulations, such as PAD.[2] Approximately one third of men and one fourth of women with known CAD also have PAD.[3] Many of CAD patients (on average 300,000 per year) enter a rehabilitation program with the objective of reducing cardiac symptoms, improving physical functioning, improving cardiovascular risk factors, reducing mortality, reducing myocardial infarctions, and improving psychological well-being.[4,5] Patients with CAD who have PAD, however, are hampered in their cardiac rehabilitation program because they either discontinue the program prematurely or are unable to achieve their target heart rate due to their limited walking distance. As a result these patients have an increased risk of cardiac events during follow-up (20%-60% increased risk for MI).[6,7]

How clinical effectiveness of a cardiac rehabilitation program is influenced by PAD, however, is still unknown. This study was performed to evaluate whether clinical effectiveness of cardiac rehabilitation was related to the presence of PAD.

MATERIALS AND METHODS

Study population

Patients who started cardiac rehabilitation at Advocate Lutheran General Hospital in Park Ridge in the United States from January 2004 to December 2004 were potentially eligible for the study (n=231). Patients were men and women, who had a myocardial infarction or who had stable angina pectoris or CAD defined by angiography or were patients who underwent coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA). All patients received a self-administered Walking Impairment Questionnaire (WIQ) by mail after they had prematurely ended or had finished the program. Of the 231 eligible patients, 59 responded to the mailed questionnaire. Because in a previous study reliability and validity of subscales of the WIQ were not influenced by the method of administration, all non-responders of the self-administered questionnaire were approached by telephone (n=172).[8] Of these 172 patients, 67 patients were reached and interviewed by telephone. Thus, in total 126 patients were included in the study. The Advocate Health Care Institutional Review Board approved the protocol and all patients gave their written informed consent.

Cardiac rehabilitation

Cardiac rehabilitation consisted of a 2 phase program following the guidelines for cardiac rehabilitation and secondary prevention programs.[9] All patients were prescribed antiplatelet medications, ß-blockers, and statins. Phase I involved integrated inpatient services, such as cardiac education that serve as the foundation for a continuum of cardiac rehabilitation interventions that began in the hospital and continued post discharge. Phase II involved a multifaceted program that included a 12 week monitored exercise training of 36 sessions (3 sessions per week) and the pursuit of modifiable risk factor reduction through education, counseling, reinforcement of medical therapies, behavior change and acceptance of personal responsibility on the part of the patient. Patients were asked to do different muscle exercises, which included a 10 minute warming up, 20 minutes of exercise on a treadmill, 20 minutes of other muscle exercise (e.g. biking, rowing, or weight training), and a 10 minute cooling down period. During exercise, patients were encouraged to reach their target heart rate. Target heart rate is a desired range of heart rate reached during a stress test. This range varies based on patient's physical condition and age and was calculated by using the Karvonen method with a range of 50%-

85% intensity in the following formula: THR = ((HRmax – HRrest) × %Intensity) + HRrest.[10] In addition, patients were encouraged to meet their target metabolic equivalents (METs), which was defined as 65-80% of the maximum METs attained during the stress test (1 MET =3.5 ml O2/kg/min). The rating of perceived exertion (RPE), on a scale of 6-20, was also used as an adjunct to heart rate and as an intensity guide for exercise training.[11] Perceived exertion is the feeling that a patient has concerning the degree of effort being exerted during his or her exercise. For example, 6 is feeling very comfortable without noticeable strain and 20 is feeling exerted to the point of being unable to continue.

Cardiac rehabilitation failure was defined as a discontinuation of the treadmill exercise program of 32 sessions or an inability to reach target heart rate.

Evaluation of PAD

The WIQ was used to assess walking ability and to diagnose PAD.[12] The WIQ was chosen in this study because prior validation and feasibility in the PAD population was demonstrated.[13] The WIQ was developed to characterize the degree of walking impairment in patients with PAD; it has three domains: walking distance, walking speed, and stair climbing.[8,12] We used a summary score for walking distance, walking speed, and stair climbing, as developed by Regensteiner and colleagues.[8]

Walking distance scores range from 0% (patients unable to walk 20 feet without stopping to rest) to 100% (patients able to walk five blocks without stopping to rest). The summary score for walking distance was derived by multiplying each individual score times the approximate distance (in feet) being assessed in a particular question, and then summing the scores. The summary score obtained was then divided by the maximum summary score possible (14080) to calculate the percent of the maximum score achieved by each patient. These responses are ranked on a scale of 0 to 4, (0=unable to do, 4=no difficulty). For example, if a patient responded with a 0 (unable to do), a 2 (some difficulty) for walking 3 blocks, and 4 (no difficulty) for the remaining 5 questions, the summary score for walking distance was calculated as: 0 (1500 ft) + 2(900 ft) + 4(600 ft) + 4(300 ft) + 4(150 ft) + 4(50 ft) + 4(20 ft) = 6280 /14080 = 0.45 = 45%.

Walking speed scores range from 0% (patients unable to walk one block slowly without stopping to rest) to 100% (patients able to jog one block without stopping to rest). The summary score for walking speed was derived in a similar fashion as that for walking distance. We estimated walking speed in miles per hour for each of the 4 questions relating to speed using recommended speed with treadmill testing for PAD patients, multiplied by the response score for a given question, and then summed the scores.[14] The total score obtained was then divided by the maximum summary score possible of 46 and expressed as a percentage.

Stair climbing scores range from 0% (patients unable to climb one flight of stairs without stopping to rest) to 100% (patients able to climb three flights of stairs without stopping to rest). The summary score for stair climbing was derived in a similar fashion as that for walking distance and speed. The maximum score possible was 288.

The threshold value of the summary scores that defined PAD in our study population was determined with a weighted mean value of cut-off values from a previous study.[15] McDermott and colleagues investigated the prevalence of unrecognized PAD with the use of the WIQ walking distance and speed scores in three groups of patients: 1) men and women with PAD identified from the non-invasive vascular laboratory (n=143); 2) unrecognized PAD, defined as men and women with a screening ankle brachial index < 0.90 in general internal medicine patients with no prior history of PAD (n=34); 3) Men and women without PAD identified from a general medicine practice (n=113). We assumed that group 1 and 2 were most representative for identifying the presence of PAD in our study population. The cut-off value for detecting PAD using the weighted mean value of the two reported walking distance scores from the two groups was 45 (95% CI, 43-46) (n=177), and the cut-off value for detecting PAD using the weighted mean value of the two reported walking speed scores from the two groups was 40 (95% CI, 39-40) (n=177). The WIQ stair climbing score was not used in the previous study and therefore also omitted in our study for the detection of the presence of PAD.

In a subset of our patient sample, we measured the ABI to diagnose PAD. The ABI is currently considered the standard tool to screen for PAD.[16] All 126 patients included in the study were invited to the hospital for additional testing on a specific date. Thirty-nine patients (31%) responded and underwent ABI measurements. The ABI was measured with a hand-held Doppler probe (8 MHz continuous wave Doppler probe) and a random-zero sphygmomanometer. For each leg, ABIs were calculated as the highest systolic blood pressure in the ankle from the right or left posterior tibial or dorsalis pedis arteries divided by the highest brachial systolic pressure. The leg with the lowest ABI was used in the analyses. PAD was defined as an ABI less than 0.90.[17]

Ten out of the 39 patients with ABI measurements had an incomplete walking distance score and 9 patients had an incomplete speed score, so that 29 patients had both a complete walking distance score and an ABI measurement and 30 patients had both a complete speed score and an ABI measurement. Theoretically, patients who refused or were unable to participate for the ABI measurement could have introduced selection bias. A comparison of the patient characteristics age, gender, smoking, diabetes mellitus, and obesity between responders and non-responders of the ABI measurements, however, were not statistically different (p>0.05).

Data analysis

The statistical significance of differences in dichotomous variables (gender, smoking, diabetes mellitus, and obesity) between the cardiac rehabilitation failure group and success group were assessed using the chi-squared test. The continuous variable age was assessed with the Students t-test. Two tailed p-values < 0.05 were considered statistically significant. Chi-squared tests were also used to compare the proportion of patients with PAD based on the walking distance score, the speed score, and ABI measurements between the cardiac rehabilitation failure group and the cardiac rehabilitation success group (two tailed p-values < 0.05 were considered statistically significant). Odds ratios (OR) of the odds favoring the presence of PAD were calculated for the cardiac rehabilitation failure group divided by odds favoring the presence of PAD in the cardiac rehabilitation success group. In addition, because age and sex are risk factors of PAD,[16] these variables may also be associated with cardiac rehabilitation failure. Therefore, we applied logistic regression models to adjust for age and gender to examine the association between cardiac rehabilitation failure and the presence of PAD, based on the walking distance score and the speed score of the WIQ. Logistic regression models based on the ABI to examine the association between cardiac rehabilitation failure and the presence of PAD were not performed, as the sample with ABI measurements was too small.

Furthermore, we evaluated whether the presence of PAD indicated by the WIQ agreed with the presence of PAD indicated by the ABI using the kappa statistic (κ). Strenght of this agreement can be interpreted as poor (κ < 0.20), fair (κ = 0.21-0.40), moderate (κ = 0.41-0.60), good (κ = 0.61-0.80), or excellent (κ = 0.81-1.0).[18] The analyses were performed in SPSS for windows (release 11.0.1; SPSS, Chicago USA).

RESULTS

Patients

Table 1 shows the patient characteristics and severity of cardiac disease. Ninety-three of 126 patients (74%) were men. The mean age was 65 years +/- 11 (range 31-91) (Table 1). Sixty-three of 126 patients (50%) had a myocardial infarction before cardiac rehabilitation, 58 of 126 patients (46%) had angina, 3 of 126 patients (2%) had an aortic valve replacement, 1 of 126 patients (1%) a mitral valve repair and 1 of 126 patients (1%) was assigned to cardiac rehabilitation for congestive heart failure. Fifty-three of 126 patients (42%) had PTCA as previous treatment, 49 of 126 patients (39%) had a CABG, and 7 of 126 patients (6%) had both treatments before cardiac rehabilitation.

Table 1: Patient characteristics and severity of cardiac disease

	n = 126	(%)
Male sex	93	74
Age (y)*	65 +/- 11 (31-91)	
Smoking (ever)	58	46
Diabetes mellitus	24	19
Obesity†	43	34
Previous diagnosis:		
Myocardial infarction	63	50
Angina	58	46
Aortic valve replacement	3	2
Mitral valve repair	1	1
Congestive heart failure	1	1
Previous treatment:		
PTCA	53	42
CABG	49	39
PTCA & CABG	7	6
None	17	13

Note.- CABG = Coronary Artery Bypass Graft; PTCA = Percutaneous Transluminal Cardiac Angioplasty
*Mean +/- SD, range in parentheses
†defined as Body Mass Index>30

Table 2 shows the cardiac rehabilitation performance of the patients. The mean measured peak heart rate level was 127 beats per minute +/- 21 (range 73-172). Sixty-four of 126 patients (51%) met their target heart rate. Estimated fitness levels ranged from 2 to 15 METs (mean 8 +/-3) and 91 of the 126 patients (72%) reached target METs. The mean number of cardiac rehabilitation sessions was 31 sessions +/- 19 (range 2-36) and 99 of 126 patients (79%) completed 32 sessions. There were 26 of 126 patients (21%) at high risk of a cardiac event, which was based on a prior stress-test with an achieved metabolic level of less than 6 METS or less than 1.4 watt/kg body weight. In our study, 51of 126 patients (40%) failed the cardiac rehabilitation and 75 of 126 patients (60%) were successful. Patient characteristics were not statistically different between the cardiac rehabilitation failure and success group (all p-values > 0.05).

Table 2: Cardiac rehabilitation performance

	n = 126	(%)
Peak heart rate (beats per minute)*	127 +/- 21 (73-172)	
Patients meeting target heart rate	64	51
METS*	8 +/- 3 (2-15)	
Patients meeting target METS	91	72
Number of sessions*		
31 +/- 19 (2-36)		
Patients who completed 32 sessions	99	79
Patients at high risk†	26	21
Successful cardiac rehabilitation ‡	75	60

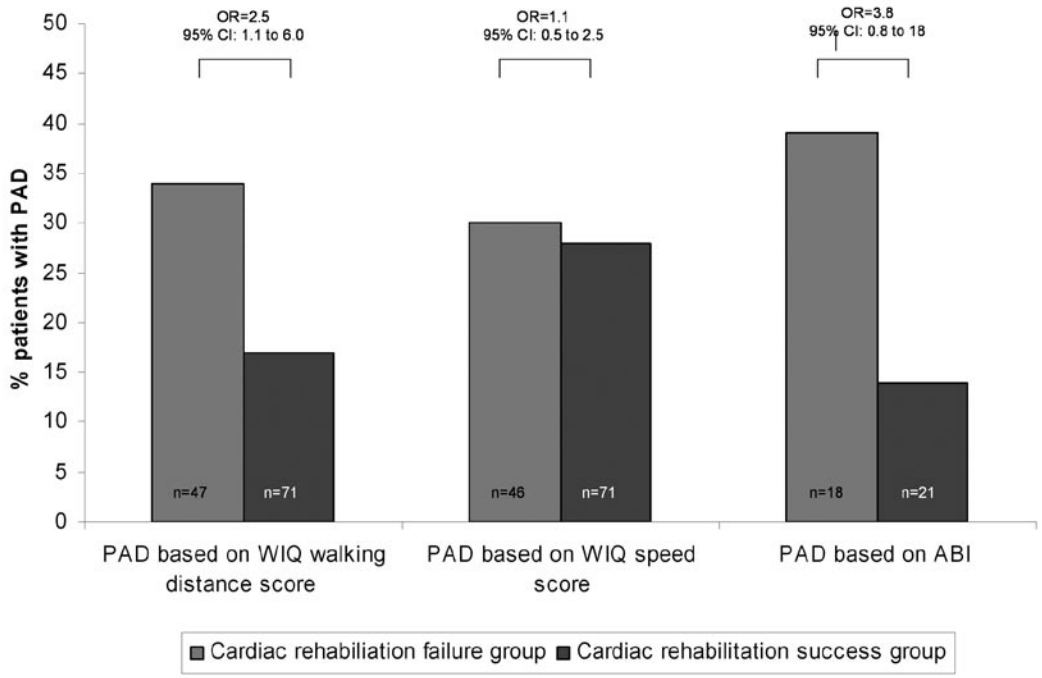
Note.- METS = metabolic equivalents
*Mean +/- SD, range in parentheses
†based on prior stress-test with METS<6 METS / <1.4 watt/kg body weight
‡successful cardiac rehabilitation was defined as a continuation of the treadmill exercise program of at least 32 sessions or the ability to reach target heart rate.

Evaluation of PAD

Based on the walking distance score, 17 of 51 patients (34%) in the cardiac rehabilitation failure group had PAD and 13 of 75 patients (17%) in the cardiac rehabilitation success group had PAD (OR 2.5; 95% CI 1.1 to 6.0, p=0.03) (Figure 1). Based on the walking speed score, 15 of 51 patients (30%) in the cardiac rehabilitation failure group and 21 of 75 (28%) in the cardiac rehabilitation success group had PAD (OR 1.1; 95% CI 0.5 to 2.5, p=0.79) (Figure 1). Based on the ABI measurements, 7 of 18 patients (39%) in the cardiac rehabilitation failure group and 3 of 21 patients (14%) in the cardiac rehabilitation success group had PAD (OR 3.8; 95% CI 0.8 to 17.9, p=0.08) (Figure 1). Cardiac rehabilitation failure, adjusted for age and sex, was significantly associated with the presence of PAD based on the walking distance score (OR 2.8; 95% CI 1.1 to 7.1, p=0.03), but not significantly associated with the presence of PAD based on the speed score (OR 1.2; 95% CI 0.5 to 2.8, p=0.72).

Table 3 shows the mean WIQ scores in the cardiac rehabilitation failure and success group. The mean walking distance score was lower in the cardiac rehabilitation failure group than in the cardiac rehabilitation success group with a borderline p-value (mean score difference 0.12; 95% CI -0.02 to 0.25, p=0.08). The mean walking speed score and the mean climbing stairs score were not significantly different between cardiac rehabilitation failure and success group (mean score difference 0.02; 95% CI

Figure 1 The presence of peripheral arterial disease based on the walking distance score and speed score of the Walking Impairment Questionnaire (n=126) and peripheral arterial disease based on the Ankle Brachial Index (n=39) in patients who participated in the cardiac rehabilitation program



Note- WIQ = Walking Impairment Questionnaire; ABI = Ankle Brachial Index; PAD = Peripheral Arterial Disease; OR = odds ratio; CI = confidence interval
* Cardiac rehabilitation failure was defined as a discontinuation of the treadmill exercise program of 32 sessions or an inability to reach target heart rate.

-0.09 to 0.14, p=0.69 and mean score difference 0.01; 95% CI -0.05 to 0.06, p=0.80 respectively) (Table 3). In addition, the mean ABI in the cardiac rehabilitation failure and success group was not significantly different between the cardiac rehabilitation failure and success group (mean index difference 0.02; 95% CI -0.14 to 0.17, p=0.87).

The agreement between the WIQ walking distance score and the WIQ speed score for indicating PAD was good (κ = 0.70). The agreement between the WIQ walking distance score and ABI and WIQ speed score and the ABI was poor (κ = 0.17 and κ = 0.07 respectively).

DISCUSSION

In our study, cardiac rehabilitation failed in almost half of the patients. We evaluated whether this failure rate was related to the presence of PAD. Our results demonstrated that in patients who failed cardiac rehabilitation, PAD was more frequently present than in patients who ended cardiac rehabilitation successfully. More specifically, after adjustment for age and gender, patients who failed cardiac rehabilitation scored less on the WIQ walking distance score. Therefore, the high number of failures

Table 3: The mean Walking Impairment Questionnaire scores (n=126) and mean Ankle Brachial Index (n=39) in cardiac rehabilitation failure and success group

	Cardiac rehabilitation failure group†	Cardiac rehabilitation success group	Mean difference	95% CI	p-value
WIQ*	(n=51)	(n=75)			
Walking distance	0.67 +/- 0.38	0.79 +/- 0.32	0.12	(-0.02 to 0.25)	0.08
Walking speed	0.57 +/- 0.29	0.57 +/ -0.39	0.02	(-0.09 to 0.14)	0.69
Climbing stairs	0.40 +/- 0.15	0.41 +/- 0.13	0.01	(-0.05 to 0.06)	0.80
ABI*	(n=18) 0.97 +/- 0.22	(n=21) 0.99 +/- 0.26	0.02	(-0.14 to 0.17)	0.87

Note.
- CI = Confidence Interval
* Mean +/- SD
† Cardiac rehabilitation failure was defined as a discontinuation of the treadmill exercise program of 32 sessions or an inability to reach target heart rate.

in cardiac rehabilitation reported in this study, as reported in many other studies, might be explained by the presence of PAD.

The association between CAD and PAD might be evident as both are manifestations of atherosclerosis and therefore patients who participate in a cardiac rehabilitation program and have PAD are likely to be limited in their walking distance and do not have optimal benefit of the program. The presence of PAD in this patient group, however, and the influence of this on the clinical effectiveness of cardiac rehabilitation was not investigated previously. Whereas the benefits of a suitable cardiac rehabilitation program in which both CAD and PAD are targeted may be apparent in success and will result in a reduction of cardiovascular risk.

The results of our study may help to develop future programs in which both CAD and PAD is targeted.

Previously, in the literature, other barriers than the presence of PAD have been reported for a successful cardiac rehabilitation, such as work, time conflicts, financial reasons, inadequate or limited insurance, lack of motivation or commitment, fear, and coexisting medical illnesses.[20] In addition, all of these barriers, including PAD, may not only be reasons for failure, but also reasons for non-attendance in a cardiac rehabilitation. Participation rates in cardiac rehabilitation are low and range from 17% to 21%.[21,22] Therefore, the total number of CAD patients with PAD that may benefit from a cardiac rehabilitation may even be higher than the actual number of CAD patients with PAD presented in our study.

In our study, the WIQ was used to indicate the presence of PAD and the ABI was used for this purpose in a subset of our patient sample. We found that cardiac rehabilitation failure was significantly associated with the presence of PAD based on the walking distance score, but not significantly associated with the presence of PAD based on the WIQ speed score or the ABI. Also previous studies demonstrated poor correlations between walking distance and the ABI.[12,19] This finding suggests the need for

a cardiac rehabilitation strategy which includes measurement of the walking distance regarding the association between the presence of PAD and the walking distance score.

A limitation of this study was the lack of the gold standard for defining the presence of PAD. Currently, contrast angiography is recommended for defining PAD.[16] Ideally, all patients should have had a contrast angiography to determine PAD. In our study, both the WIQ and ABI were used to indicate PAD and showed face-validity as both measures indicated a higher proportion of patients with PAD in the cardiac rehabilitation failure group than in the cardiac rehabilitation success group.

Another limitation may be that our 126 study participants were only a subset of a total cohort of 231 patients, which potentially could have biased the results. The differences between the proportion failures and successful patients of the cardiac rehabilitation, however, were not statistically different between patients who participated and patients who did not participate in our study. In addition, our study sample size was sufficient to detect a difference in the presence of PAD between the cardiac rehabilitation failure group and the cardiac rehabilitation success group of the patients who participated in the cardiac rehabilitation.

Based on the results of our study, diagnosing PAD in patients eligible for cardiac rehabilitation seems important as the presence of PAD influenced the effectiveness of cardiac rehabilitation negatively and emphasizes the need to explore alternative strategies to diagnose and treat PAD in patients in cardiac rehabilitation. A new cardiac rehabilitation program in which the diagnosis and the treatment of PAD if needed are included could potentially increase the success of the program and improve cardiovascular risk reduction.

In conclusion, our results suggest that the clinical effectiveness of cardiac rehabilitation was inversely related to the presence of PAD, which means that patients with PAD have less benefit of the program and are at higher risk of future cardiac events. The treatment management in patients with both PAD and CAD should be with a new combined cardiovascular rehabilitation program, which could potentially increase the success of the program and improve cardiovascular risk reduction.

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7 COST-EFFECTIVENESS OF NEW CARDIAC AND VASCULAR REHABILITATION STRATEGIES FOR PATIENTS WITH CORONARY ARTERY DISEASE

COST-EFFECTIVENESS OF NEW CARDIAC AND VASCULAR REHABILITATION STRATEGIES FOR PATIENTS WITH CORONARY ARTERY DISEASE

ABSTRACT

Purpose: Evaluating the relative cost-effectiveness of new rehabilitation strategies which include the diagnosis and treatment of peripheral arterial disease (PAD) in patients with coronary artery disease (CAD) undergoing cardiac rehabilitation.

Materials and methods: We developed a Markov decision model to compare the following treatment strategies: 1) Cardiac rehabilitation; 2) Diagnostic work-up if cardiac rehabilitation fails followed by revascularization for PAD if needed; 3) Diagnostic work-up for PAD in all patients prior to cardiac rehabilitation and revascularization for PAD if needed; 4) A combined cardiovascular rehabilitation. The best-available evidence was retrieved from the literature and combined with primary data from 231 patients. Quality-adjusted-life years (QALYs), life-time costs, incremental cost-effectiveness ratios (ICER), and gain in net health benefits (NHB) were calculated. A threshold willingness-to-pay of $75 000 was used.

Results: Cardiovascular rehabilitation was the most attractive with an ICER of $16 461 per QALY gained and a gain in NHB of 0.06 compared to current practice. In an analysis without this strategy, a diagnostic work-up if cardiac rehabilitation fails followed by revascularization for PAD if needed was most beneficial with an ICER of $49 468 per QALY gained and a gain in NHB of 0.02 compared to current practice.

Conclusions: A combined cardiovascular rehabilitation, or a diagnostic work-up in patients who fail cardiac rehabilitation followed by revascularization for PAD if needed, could potentially decrease secondary cardiac events and save society millions of dollars.

BACKGROUND

Coronary artery disease (CAD) is the leading cause of mortality and morbidity in the United States.[1] Millions of Americans have a history of myocardial infarction or experience angina pectoris1. Many of these patients (on average 300,000 per year) enter a rehabilitation program and those who have undergone re-vascularization procedures undergo cardiac rehabilitation with the objective of improving exercise tolerance, symptoms, serum lipid levels, and psychosocial well-being, while reducing cardiac risk factors and mortality.[2, 3] Published guidelines for cardiac rehabilitation and secondary prevention programs advocate a multifaceted program that includes a monitored 12 weeks exercise training of 36 sessions (3 sessions per week) and the pursuit of modifiable risk factor reduction through education, counseling, reinforcement of medical therapies, behavior change and acceptance of personal responsibility on the part of the patient.[4]

Patients with CAD, however, frequently have peripheral arterial disease (PAD). PAD hinders the cardiac rehabilitation program because patients are unable to achieve their target heart rate due to their limited walking distance. Almost half of the patients who start cardiac rehabilitation do not complete the program successfully,[5] in large part due to the presence of PAD, and these patients are at increased risk for cardiac events during follow-up (20%-60% increased risk for MI).[6, 7] Therefore, a diagnostic work-up if cardiac rehabilitation fails followed by revascularization for PAD if needed, or a work-up and revascularization prior to cardiac rehabilitation, may improve the results. Alternatively, rehabilitation that focuses on improvement of both target heart rate and walking distance may be more effective because it benefits patients who have both CAD and PAD.

The aim of the present study was to evaluate the effectiveness, costs, and relative cost-effectiveness from the societal perspective of new rehabilitation strategies which include the diagnosis and treatment of PAD in patients with CAD undergoing cardiac rehabilitation.

METHODS

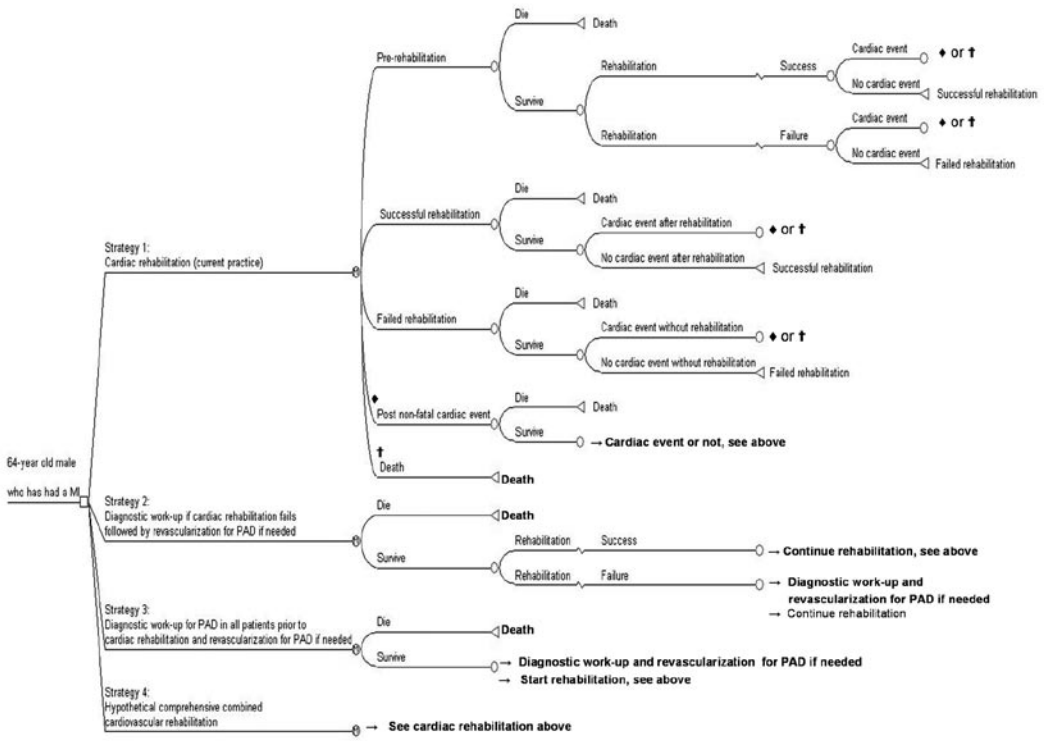
Model structure

A Markov decision model was developed to compare current cardiac rehabilitation with new rehabilitation strategies for patients with CAD.[8, 9] Our primary cohort for analyses (the base-case) consisted of 64-year old male patients who entered a cardiac rehabilitation program.

The strategies in the model were 1) Cardiac rehabilitation (i.e., current practice); 2) Cardiac rehabilitation; if rehabilitation fails diagnostic work-up for PAD and if needed revascularization, after which cardiac rehabilitation is continued; 3) Diagnostic work-up for PAD and if needed revascularization, after which cardiac rehabilitation is started; 4) A comprehensive combined cardiovascular rehabilitation program focused on achieving both target heart rate and improving walking distance.

Figure 1 shows a schematic representation of the model. In the cardiac rehabilitation strategy, patients entered the program which they either completed successfully or they failed. If failure due to PAD occurred, no intervention took place and patients were followed in the outpatient clinic. Cardiac rehabilitation failure was defined as a discontinuation of the treadmill exercise program of 32 sessions or disability to reach target heart rate (individually determined during a stress test prior to cardiac rehabilitation). In follow-up, patients experienced a fatal or non-fatal cardiac event (i.e., defined as acute angina or non-fatal myocardial infarction) or they died from non-cardiac causes.

Figure 1.



Schematic simplified representation of the Markov model. It shows four different rehabilitation strategies. Every strategy contains health states in which a patient can remain for more than one cycle. These are pre-rehabilitation (from which every patient starts), successful rehabilitation, failed rehabilitation, post non-fatal cardiac event, and death (i.e. cardiac death and non-cardiac death). All health states are only demonstrated in the upper strategy for simplification.

MI = Myocardial infarction; PAD = peripheral arterial disease; CAD = coronary artery disease

In the second strategy, patients also entered a cardiac rehabilitation program but now if patients failed, a diagnostic work-up with diagnostic subtraction angiography or magnetic resonance angiography (proportion 1:1) was performed. If PAD was present, the lesion was treated with percutaneous intervention or bypass surgery depending on disease severity and level of disease. Suprainguinal percutaneous transluminal angioplasty (PTA) with stent placement, aorto-iliac grafting, infrainguinal PTA, and femoro-popliteal bypass were modeled as revascularization procedures. After revascularization, some patients had complications or procedural failures and were unable to continue cardiac rehabilitation, whereas most patients continued with their cardiac rehabilitation program.

In the third strategy, all patients underwent a diagnostic work-up prior to cardiac rehabilitation. If patients had PAD, a revascularization with PTA or bypass surgery was performed prior to cardiac rehabilitation.

In the fourth strategy, patients entered a comprehensive combined cardiovascular program. In this program we assumed that patients performed maximum arm exercise (e.g. rowing, weightlifting) with a peak heart rate or an arbitrary metabolic equivalent (MET) level (1 MET = 3.5 ml O2/kg/min),

such as 5 METs to reach target heart rate. Furthermore, patients performed submaximal individual treadmill exercise with a workload which increased patient's walking ability.

For each of the four strategies, the model kept track of time and costs spent in one of the following health states: (a) pre-rehabilitation; (b) successful rehabilitation; (c) failed rehabilitation; (d) post non-fatal cardiac event; and (e) cardiac death or non-cardiac death. A Markov cycle tree was updated every 6 months after which patients' clinical status and costs were estimated to model life-time health benefits and costs.

Data Sources

Effectiveness and cost data for the model were retrieved from the literature and from primary data collection. Table 1 and 2 show estimates from the best-available evidence of the included variables with probability distributions representing the uncertainty around the estimates and the data sources. Original patient data was collected in Lutheran General Hospital, Chicago, U.S., and included data from 231 consecutive men and women who started cardiac rehabilitation from January 2004 - December 2004. Of the 231 patients, 125 patients (54%) completed cardiac rehabilitation successfully, 97 patients (42%) failed cardiac rehabilitation, and 9 patients (4%) were lost to follow-up. Of the 9 patients who were lost to follow up, half were assumed to belong to the cardiac rehabilitation failure group and the other half to the success group, so that finally 56% (54%+2%) were assumed to complete cardiac rehabilitation successfully.

Effectiveness

In addition to estimates derived from the literature and the hospital database that were included directly in the model, some estimates were recalculated and several assumptions were needed. Hazard rates for fatal- and non-fatal cardiac events during follow-up for patients with and without cardiac rehabilitation, were calculated from probabilities derived from a systematic review of Taylor and colleagues (Table 1).[10]

Long-term life expectancy was calculated on the basis of age-and sex-specific mortality rates from standard U.S. life-tables of the general population.[11] In addition, life-expectancy was adjusted for quality of life (i.e., Quality-Adjusted-Life Years (QALYs) using health-related quality-of-life weights (Table 2)). To estimate the quality-of-life weight prior to rehabilitation and for successful completion of the program, we used the weighted average of health-related quality-of-life weights based on the literature.[12, 13] For patients who failed cardiac rehabilitation, quality-of-life weights were not available. We assumed that these patients had the same quality of life as prior to rehabilitation as they did not experience any benefit from the program (Table 2).

The proportion of patients who failed cardiac rehabilitation due to PAD was based on the Ankle-Brachial-Index (ABI) measured in a subset of our patient sample. All 231 patients were invited to the hospital for additional testing on a specific date, of which 39 patients responded. The patient characteristics between the subset and the non-responders were not statistically different ($p > 0.05$). In the responders, the ABI was measured and PAD was defined as an ABI less than 0.90.[14] The leg with the lowest ABI was used in the analyses.

In strategies that included revascularization for PAD, we assumed that in the majority of patients (95%) revascularization was possible and that 90% of these patients would benefit from treatment. In our patient sample, 7 out of 39 patients (18%) failed cardiac rehabilitation due to PAD, therefore we mod-

Table 1: Data included in the Markov model on rehabilitation strategies for patients with coronary artery disease.

Variable	Base Case Value	Distribution	Range	Literature or Database Source
PROBABILITIES CARDIAC REHABILITATION				
Success current cardiac rehabilitation	0.56	Beta	0.1 - 0.9	ALGH
Success cardiac rehabilitation after treatment PAD	0.71	Beta	0.1 - 0.9	see text
Failure cardiac rehabilitation due to PAD	0.18	Beta	0.05 - 0.75	ALGH
Diagnosis PAD before cardiac rehabilitation starts	0.26	Beta	0.05 – 0.75	ALGH
Success comprehensive combined cardiovascular rehabilitation	0.70	Beta	0.41-0.99	see text
6-MONTH RATES OF EVENTS DURING FOLLOW-UP				
Cardiac event after rehabilitation (fatal and non-fatal)	0.025	Beta	0.01 – 0.03	[10], see text
Cardiac event without rehabilitation (fatal and non-fatal)	0.029	Beta	0.01 – 0.04	[10], see text
Fatal cardiac event after rehabilitation	0.012	Beta	0.005 – 0.02	[10], see text
Fatal cardiac event without rehabilitation	0.013	Beta	0.005 – 0.02	[10], see text
PROBABILITIES PAD STATUS				
Suprainguinal disease conditional on the presence of PAD	0.56	Beta	0.12 - 0.85	[27]
Suprainguinal lesion is suitable for angioplasty	0.51	Beta	0.43 - 0.59	[27, 28]
Infrainguinal lesion is suitable for angioplasty	0.18	Beta	0 - 0.25	[27, 28]
Lesion is suitable for surgery‡	0.95	Beta	0 - 0.99	see text
Aorto-iliac lesion is occlusive vs. stenotic	0.20	Beta	0 - 0.5	[29]
Femoro-popliteal lesion is occlusive vs. stenotic	0.36	Beta	0 - 0.6	[30]
Vein is available for bypass surgery vs. PTFE	0.20	Beta	0 - 0.5	ALGH
MORTALITY RATE FOR PAD PROCEDURES AND IMAGING				
Iliac PTA with selective stent placement	0.013	Beta	0 - 0.037	[31]
Femoral or popliteal PTA	0.025	Beta	0 - 0.264	[32]
Aortic bifurcation grafts	0.040	Beta	0 – 0.10	[33]
Femoro-popliteal or infrapopliteal bypass	0.047	Beta	0.008 - 0.127	[32]
Diagnostic imaging (angiography and magnetic resonance imaging)	0.00033	Beta	0.00029- 0.00162	[34, 35]
*PROBABILITIES SYSTEMIC COMPLICATIONS OF PAD PROCEDURES**				
Iliac PTA with selective stent placement	0.013	Beta	0 -0.035	[31]
Femoral or popliteal PTA	0.013	Beta	0.002 - 0.11	[32]
Aortic bifurcation grafts	0.083	Beta	0 - 0.1	[31]
Femoro-popliteal or infrapopliteal bypass	0.085	Beta	0.027- 0.13	[32]
6-MONTH PATENCY IN PATIENTS WITH PAD				
Iliac PTA with selective stent placement †				
Stenosis	0.9	Beta	0.70 - 0.99	[31]
Occlusion	0.80	Beta	0.70 - 0.99	[31]
Femoro or popliteal PTA without stent placement				
Stenosis	1.0	Beta	0.98 - 1.0	[36]
Occlusion	0.88	Beta	0.81 - 0.94	[36]
Femoro or popliteal PTA with stent placement				
Stenosis	1.0	Beta	0.99 - 1.0	[36]
Occlusion	0.99	Beta	0.92 - 1.0	[36]
Aortic bifurcation grafts	0.98	Beta	0.98 - 0.99	[37]
Femoro-popliteal or femoroinfrapopliteal bypass				
Autologous vein above-knee anastomosis	0.95	Beta	0.90 - 0.99	[38, 39]
Autologous vein below-knee anastomosis	0.94	Beta	0.93 - 0.95	[40]
PTFE, above-knee anastomosis	0.87	Beta	0.84 - 0.90	[40, 41]
PTFE, below knee anastomosis	0.70	Beta	0.65 - 0.75	[40, 41]

ALGH: Advocate Lutheran General Hospital; PTFE = Poly Tetra Fluor Ethylene, PTA = Percutaneous Transluminal Angioplasty, PAD = Peripheral Arterial Disease

*Systemic complication is defined as all events that occurred within 30 days after the procedure and that required additional medical care.

†Patency estimates for iliac PTA with selective stent placement have been shown to equal those for iliac PTA with primary stent placement.[41]

‡ In the Markov model, we assumed that 5% of the lesions were not suitable for surgery.

eled that 15% (i.e., 18% * 95% * 90%) underwent succesful revascularization for PAD and subsequently continued their cardiac rehabilitation program. Thus, including the possibility of revascularization for PAD in the cardiac rehabilitation strategy, in total 71% (i.e., 56% plus 15%) of all patients completed the cardiac rehabilitation program successfully.

In the comprehensive combined cardiovascular rehabilitation strategy, we assumed that the success rate of rehabilitation compared to current practice increased by 25%. This assumption was based on an 80% success rate as a result of the vascular component of the combined rehabilitation program in patients who would otherwise fail due to PAD. Thus, in this strategy an additional 14% (i.e., 80% of 18%) completed the program successfully. Therefore, in total 70% (i.e., 56% plus 14%) completed the new program successfully; hence, the increase in success rate of 25% (i.e., 70% versus 56%).

COSTS

Costs included in the model incorporated medical and non-medical costs and were assessed from the societal perspective (Table 2). Medical costs included costs of all diagnostic and therapeutic procedures, cardiac rehabilitation, costs for personnel, materials, equipment, associated hospital admissions during 6 months follow-up, and overhead. These costs were derived from the financial department of Lutheran General Hospital.

Non-medical costs included transportation costs and patient time costs. Transportation costs included parking costs and mean estimated gasoline costs. Patient time costs were determined by multiplying the hourly wage rate ($18.55/hour) by the number of hours or days spent in the hospital.[15] Time spent in the hospital was derived from our hospital database (e.g. cardiac rehabilitation 36 hours (60 min * 36 sessions) and a bypass procedure was on average 6.5 days).

Costs of current practice (cardiac rehabilitation) included scheduled cardiac rehabilitation visits, a stress test, follow-up visits, transportation costs, and patient time costs. Costs of the comprehensive combined cardiovascular rehabilitation program were assumed to be higher than for current practice (Table 2) as a cardiovascular program is more extensive and needs to be developed.

To take into account time preference, future costs were discounted at the currently recommended nominal discount rate of 3% per year.[16] All costs were converted to the year 2005 U.S. dollars by using the medical care specific consumer price index obtained from the Bureau of labour Statistics.[17]

ANALYSIS

Quality-adjusted-life expectancy, life time costs, and incremental cost-effectiveness ratios (i.e., additional costs divided by quality-adjusted-life-years gained) were calculated for all four strategies. In a second analysis, the hypothetical comprehensive combined cardiovascular rehabilitation was excluded and we focused on currently existing strategies only. Strategies were ordered according to increasing effectiveness (QALYs). A strategy was considered dominated if another strategy was both more effective and less costly. A strategy was considered extended dominated if another strategy achieved more effectiveness at a lower incremental cost-effectiveness ratio. After eliminating dominated and extended dominated strategies the incremental cost-effectiveness ratios (ICERs) were calculated as the difference in mean lifetime costs divided by the difference in mean QALYs for each strategy compared to the next best non-dominated strategy.[18]

Table 2: Health related quality of life and costs in U.S. Dollars.

Variable	Base Case Value	Distribution	Range	Literature or Database Source
HEALTH-RELATED QUALITY OF LIFE WEIGHTS				
Pre-rehabilitation*	0.83	Uniform	0.5 - 0.99	[12, 13]
After failed cardiac rehabilitation	0.83	Uniform	0.5 - 0.99	See text
After successful cardiac rehabilitation	0.98	Uniform	0.8 - 0.99	[12, 13, 42, 43]
After non-fatal cardiac event	0.83	Uniform	0.5 - 0.99	[12, 13]
Systemic complications†	0.72	Uniform	0.6 - 0.90	[44]
COSTS (US DOLLARS)§				
REHABILITATION (6 months)				
Scheduled visits cardiac rehabilitation	3,112			ALGH
Stress test	95			ALGH
Follow-up visit	75			ALGH
Transportation costs	117			ALGH
Patient time costs	481			ALGH [17]
Total costs Cardiac rehabilitation if successfully completed	3,880	Lognormal	1,940 –5,820	ALGH
Total costs Cardiac rehabilitation if patient failed the program ¶	3,289	Lognormal	1,645 - 4,936	ALGH
Total costs comprehensive cardiovascular rehabilitation if successfully completed	5,820	Lognormal	2,910 - 8,730	See Text
Total costs comprehensive cardiovascular rehabilitation if patient failed the program ¶	4,934	Lognormal	2,467 - 7,401	See Text
Post-Program after rehabilitation (per year)	1,257	Lognormal	629 -1,886	[45]
DIAGNOSIS FOR PAD				
Diagnostic angiography/imaging‖	778	Lognormal	389 - 1,167	ALGH
REVASCULARIZATION FOR PAD				
Aortic bifurcation grafts	32,942	Lognormal	16,471 - 49,413	ALGH
Iliac PTA with selective stent placement ‡	9,618	Lognormal	6,369 - 12,739	[41, 46, 47]
Femoro-popliteal or infrapopliteal bypass	13,932	Lognormal	6,966 - 20,898	ALGH
Femoral or popliteal PTA	5,305	Lognormal	1,528 - 8,906	[47]
SYSTEMIC COMPLICATIONS AFTER REVASCULARIZATION FOR PAD	12,430	Lognormal	8,269 - 16,539	[47]
Short-term costs	13,715	Lognormal	6,361 - 9,083	[48]
Annual long-term costs	14,783	Lognormal	4,580 - 25,445	[47]
Mortality from revascularization procedures				
RECURRENT EVENTS				
Non-fatal cardiac event first year	18,589	Lognormal	9,295 - 27,884	[45]
Non-fatal cardiac event annually thereafter	7,500	Lognormal	3,750 - 11,250	[45]
Fatal cardiac event	20,971	Lognormal	10,486 - 31,457	[45]

ALGH = Advocate Lutheran General Hospital; PTA = Percutaneous Transluminal Angioplasty; PAD = Peripheral Arterial Disease.
* Values based on responses on the EuroQol-questionaire [49, 50].
† Average Time Trade-off value among survivors of a myocardial infarction, used as a proxy for the effect on quality of life of a systemic complication[44].
‡ Assumes that in 43% of the cases a stent is placed [41].
§ Costs were converted to the year 2005
¶ Based on the average number of sessions patients completed in ALGH
‖ Costs are average costs of MRA and DSA because they were performed in the same proportion in ALHG.

Furthermore, we transformed costs and QALYs into one comprehensive outcome measure: the net health benefit (NHB).[9, 19, 20] The NHB was defined as lifetime effectiveness (QALYs) minus lifetime costs ($), the latter divided by the societal willingness-to-pay (WTP) threshold to save one QALY ($/QALY). The NHB is expressed in QALY-equivalents. Published estimates for WTP ranged from $20 000 to $100 000 per QALY gained. In our analysis we considered $75 000 per QALY gained as a commonly accepted threshold and varied the WTP between $50 000 and $100 000 in sensitivity analyses.[20, 21] For each of the three new strategies considered we calculated the gain in NHB compared to the NHB of current practice.[22]

To explore the effect of uncertainty in our parameter estimates, we performed extensive one-way, two-way, and multi-way sensitivity analysis. Using probabilistic sensitivity analysis (second order Monte Carlo simulation), the uncertainty around the outcomes of the strategies was assessed[9, 23] by picking at random a value from each of the distributions of the parameter values, running the model with these values to get one set of outcome values, and repeating this 100 000 times.[8]

In value of information analysis we determined whether more information from future research is necessary to decrease the remaining uncertainty.[24] More research is not justified if the expected costs of further research exceed the expected benefit of that study. To estimate the total expected value of perfect information (EVPI) per patient, we calculated for each of the 100,000 Monte Carlo simulations from the probabilistic sensitivity analysis 22 the NHB of the optimal strategy per simulation, which is the expected NHB with perfect information. The EVPI is the difference between the mean expected NHB with perfect information from the probabilistic sensitivity analysis and the mean NHB with current information from the primary analysis. Next, we estimated the population EVPI, which is the total EVPI per patient multiplied by the expected lifetime of the technology and multiplied by the annual number of future patients expected to benefit from more research of the optimal strategy adjusted for the discount rate.[22] Based on the annual number of patients who undergo cardiac rehabilitation in the United States, we assumed that the annual population that could benefit from future clinical research on new rehabilitation strategies would be 300,000. Expressing patient and population EVPI in dollars the NHB was reframed in terms of Net Monetary Benefit (NMB = NHB*WTP) which enables comparison with research costs. The NMB is the maximum amount that we should spend on future research to decrease current uncertainty.

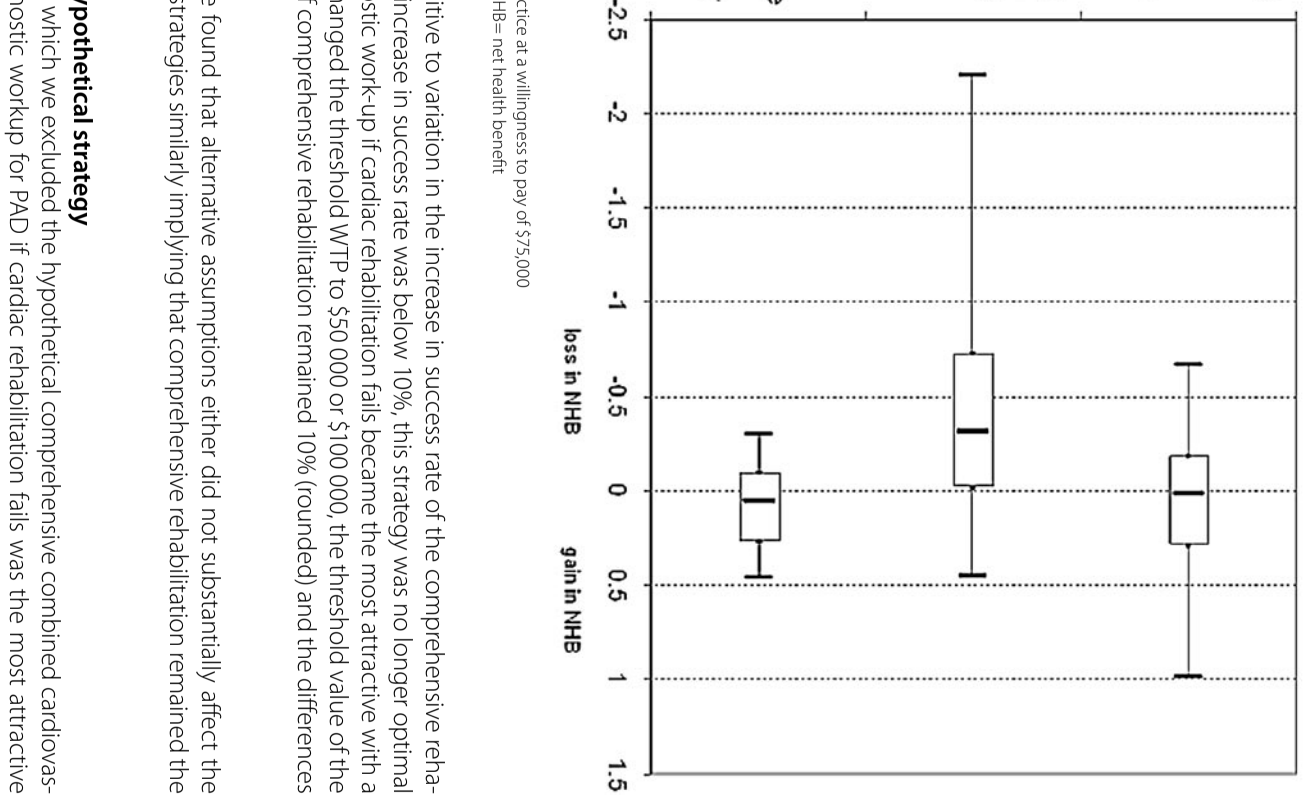
RESULTS

Analysis of all strategies

Using our best estimates in the base-case analysis, comprehensive combined cardiovascular rehabilitation was the most attractive strategy with an ICER of $16,461 per QALY gained (Table 3). The NHB of this new strategy was 3.9 at a WTP of $75,000 (Table 3). The gain in NHB compared to current practice was 0.06 and the 95% confidence intervals included 0 (Figure 2), which implies uncertainty around the outcome.

Intermediate outcomes presented in Table 4, showed that in a hypothetical cohort of 10,000 patients, the number of patients with a cardiac event during follow-up was lowest when a diagnostic work-up for PAD was performed in all patients. This benefit was diminished, however, by an increased number of patients with peri-procedural morbidity and mortality related to the PAD revascularization procedure. Furthermore, Table 4 showed that the combined cardiovascular rehabilitation program saved 45 cardiac events per 10 000 patients. Thus, with 300 000 eligible patients for cardiac rehabilitation per year, this new rehabilitation program may cost society 582 million dollars (assuming $1940 additional expense per patient), whereas it may save society $27 billion due to a decrease in cardiac events (approximately 1350 prevented cardiac events in 300.000 patients * $20 000).

Figure 2. Gain in net health benefit with 95% confidence intervals of new rehabilitation



strategies compared to current practice at a willingness to pay of $75,000
PAD = peripheral arterial disease; NHB= net health benefit

The outcomes were sensitive to variation in the increase in success rate of the comprehensive rehabilitation program. If the increase in success rate was below 10%, this strategy was no longer optimal and performing a diagnostic work-up if cardiac rehabilitation fails became the most attractive with a NHB of 3.7 QALYs. If we changed the threshold WTP to $50 000 or $100 000, the threshold value of the increase in success rate of comprehensive rehabilitation remained 10% (rounded) and the differences in NHB were small.

For other parameters, we found that alternative assumptions either did not substantially affect the outcomes or affected all strategies similarly implying that comprehensive rehabilitation remained the most attractive strategy.

Analysis without the hypothetical strategy

In our second analysis, in which we excluded the hypothetical comprehensive combined cardiovascular rehabilitation, diagnostic workup for PAD if cardiac rehabilitation fails was the most attractive with an ICER of $49 468 per QALY gained (Table 3). The NHB of this strategy was 3.9 at a WTP of $75,000 (Table 3). The gain in NHB compared to current practice was 0.02 and the 95% confidence intervals included 0 (Figure 2), which implies uncertainty around the outcome.

Table 3: Cost, clinical effectiveness, and cost-effectiveness of (new) rehabilitation strategies for patients with coronary artery disease

	Total Lifetime Costs*†	Quality-Adjusted Life Expectancy* (years)	Net Health Benefit (WTP = $75,000)	Incremental Costs per Quality-Adjusted Life Year ($/QALY) considering all 4 strategies *	Incremental Costs per Quality-Adjusted Life Year ($/QALY) considering currently available strategies (1,2,3) *
STRATEGY 1: Cardiac rehabilitation (Current practice)	32,413	4.31	3.87	_	_
STRATEGY 2: Diagnostic work-up if cardiac rehabilitation fails followed by revascularization for PAD if needed	35,471	4.37	3.90	Dominated‡§	49,468
STRATEGY 3: Diagnostic work-up for PAD in all patients prior to cardiac rehabilitation and revascularization for PAD if needed	49,551	4.20	3.54	Dominated‡§	Dominated‡§
STRATEGY 4: Hypothetical comprehensive combined cardiovascular rehabilitation	33,634	4.38	3.93	16,461	n/a

QALY = Quality-Adjusted- Life Year; PAD = Peripheral Arterial Disease; WTP = Willingness To Pay; n/a = not applicable; Net health benefit = QALYs – (lifetime costs/ WTP)
* Future costs and life years were discounted at 3% per year
† 2005 US dollars
‡ More expensive and less effective than other strategy
§ Compared to the next best strategy

Table 4: Intermediate Outcomes: number of cardiac events* during follow-up and number of peri-procedural complications in the base-case analysis in a hypothetical cohort of 10,000 patients.

Per 10,000 patients	Cardiac event during follow-up No. of patients	Peri-procedural complications and death from PAD revascularization procedure No. of patients
STRATEGY 1: Cardiac rehabilitation	2700	0
STRATEGY 2: Diagnostic work-up if cardiac rehabilitation fails followed by revascularization for PAD if needed	2659	106
STRATEGY 3: Diagnostic work-up for PAD in all patients prior to cardiac rehabilitation and revascularization for PAD if needed	2644	122
STRATEGY 4: Hypothetical comprehensive combined cardiovascular rehabilitation	2655	0

Cardiac event = acute angina or non-fatal myocardial infarction
PAD = Peripheral Arterial Disease
* unrelated to PAD revascularization

In one-way sensitivity analysis, we varied the "probability that PAD is the cause of cardiac rehabilitation failure". Below a probability of 0.07, current practice was the preferred strategy with a NHB of 3.9 QALYs. In a two-way sensitivity analysis where we changed both the "probability that PAD is the cause of cardiac rehabilitation failure" and the WTP to $50 000, current practice was the preferred strategy below a threshold probability of 0.4 with a NHB of 3.7 QALYs. Doing a diagnostic work-up for PAD in all patients prior to the cardiac rehabilitation program would not be beneficial, which was mainly due to the higher costs of the diagnostic imaging and due to the peri-procedural complications. Multi-way sensitivity analysis demonstrated that for a WTP of $50 000 with a 50% reduction in peri-procedural complications, 50% increase that the patient has PAD, and below a threshold of 0.10 that PAD is the cause of cardiac rehabilitation failure, current practice was the preferred strategy with a NHB 3.6 QALYs. Performing a diagnostic work-up for PAD prior to cardiac rehabilitation in all patients was dominated by all other strategies.

For other parameters, we found that alternative assumptions either did not substantially affect the outcomes or affected all strategies similarly. If we lowered, for example, the original estimated rate of cardiac events after cardiac rehabilitation, the ICERs decreased for all strategies. Furthermore, varying the costs of fatal- and non-fatal cardiac events between 50% and 150% of the original estimates affected all strategies similarly and did not change the results of the ICERs.

Value of information analysis

In the analysis which included all strategies, the total EVPI per patient was $2 327 using a WTP of $75 000. This implies that an infinitely large future study is expected to increase the NMB per patient with $2 327 for the optimal rehabilitation strategy. With the annual estimated number of patients that undergo cardiac rehabilitation of 300,000, an effective lifetime of a new rehabilitation strategy of 10 years, and a discount rate of 3%, the population EVPI was $6 billion.

DISCUSSION

In this study, we evaluated whether patients with CAD who currently enter a cardiac rehabilitation program would benefit more from the program if treatment for PAD is considered. The results suggest that a hypothetical comprehensive combined cardiovascular approach is cost-effective compared to current practice. Although a comprehensive combined cardiovascular rehabilitation is more expensive, the success rate of this new rehabilitation strategy is expected to be higher, preventing additional events in CAD patients during follow-up, which would lead to a gain in QALYs. When we excluded this hypothetical strategy from the analysis, the strategy with diagnostic work-up if cardiac rehabilitation fails followed by revascularization for PAD if needed was the most attractive. A strategy that included a diagnostic work-up for PAD in all patients prior to the cardiac rehabilitation program with revascularization if needed, did not increase QALYs compared to current practice.

Current rehabilitation programs in the United States and in Western European countries consist of either cardiac rehabilitation for patients with CAD or vascular rehabilitation for patients with PAD. A combined program does not exist. Vascular programs range from hospital-based walking on a treadmill to home-based walking in the community until a mild or moderate level of pain is reached. These programs do not induce patients' target heart rate. We showed that it is attractive to develop a new rehabilitation program in which cardiac rehabilitation and vascular programs are combined, or revascularisation for PAD is considered, to decrease the failure rate of cardiac rehabilitation.

Due to continuously escalating medical costs, third-party payers demand evidence of cost-effectiveness and cost-related benefits of health care services and programs. With the new comprehensive combined cardiovascular rehabilitation strategy or the strategy with diagnostic work-up if cardiac rehabilitation fails followed by revascularization for PAD if needed, many secondary events can be avoided in patients with CAD. This new rehabilitation program needs to be developed, may be more extensive, and therefore may initially cost more. With 300,000 eligible patients for cardiac rehabilitation per year, this new rehabilitation program may cost society a little over half a billion dollars, whereas it may save society $27 billion due to a decrease in cardiac events. Nevertheless, we must interpret these results with caution because of the remaining uncertainty in our analysis.

Future clinical research could reduce the uncertainty and patients could potentially benefit from more precise estimates of test characteristics, costs, and treatment effects. To assess whether the remaining uncertainty justifies future research, we performed a value of information analysis. The large population EVPI of $6 billion suggests that a substantial investment in future research would be justified.

One of the limitations of this study was that certain assumptions were needed in evaluating the rehabilitation strategies in a Markov model, which may have affected our results. In the analysis of all strategies, the preferred strategy depends on the assumption of the increase in success rate of the comprehensive combined cardio-vascular rehabilitation. If we assumed a lower increase in success rate of the comprehensive combined cardio-vascular rehabilitation, diagnostic work-up if cardiac rehabilitation fails followed by revascularization for PAD if needed would be beneficial. Thus, a combination of a vascular and a cardiac program or a diagnostic workup for PAD if cardiac rehabilitation fails would be more attractive than cardiac rehabilitation alone. For many other assumptions, we demonstrated that varying the parameter values did not change the results substantially or changed the results for all strategies similarly while the conclusions remained the same. Another limitation of our study was the small subset of our patient sample who participated in the follow-up ABI measurement to determine the percentage failures due to PAD in our study group. However, the patient character-

istics between the responders and non-responders were not significantly different and varying the percentage of failures due to PAD in a sensitivity analysis, we demonstrated that the results remained the same.

Cardiac rehabilitation programs remain underused in many countries. For example, in the U.S. only 10 to 20 percent of 2 million eligible patients per year who experienced a myocardial infarction or underwent cardiac revascularization procedures participated in a cardiac rehabilitation program.[2] Previous studies reported that factors such as poor patient motivation or co-existing illnesses were related to non-attendance of the cardiac rehabilitation program.[25,27] Many patients among non-participants could be physically inactive because of PAD, which could reduce patient's motivation to participate in a cardiac rehabilitation program and emphasizes the need to explore alternative strategies to diagnose and treat PAD in patients in cardiac rehabilitation programs.

In conclusion, the results suggest that a more aggressive approach to the diagnosis and treatment of PAD in CAD patients undergoing cardiac rehabilitation is warranted. A combined cardiovascular rehabilitation program, or if this is unavailable a diagnostic work-up for PAD in patients who fail cardiac rehabilitation followed by revascularization if needed, could potentially decrease secondary cardiac events and save society millions of dollars.

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8 VALUE OF THE DUPLEX WAVEFORM AT THE COMMON FEMORAL ARTERY FOR DIAGNOSING OBSTRUCTIVE AORTOILIAC DISEASE

VALUE OF THE DUPLEX WAVEFORM AT THE COMMON FEMORAL ARTERY FOR DIAGNOSING OBSTRUCTIVE AORTOILIAC DISEASE

ABSTRACT

Purpose: To evaluate the accuracy, predictive value, and observer agreement of the duplex ultrasound waveform at the common femoral artery as a marker of significant aortoiliac disease in a large group of consecutive patients who underwent a diagnostic workup for peripheral arterial disease in a vascular unit.

Materials and methods: In 191 consecutive patients (381 aortoiliac segments), we classified the duplex ultrasound waveform at the common femoral artery as triphasic, biphasic, sharp monophasic, or poor monophasic. The waveforms were then compared with the findings of magnetic resonance angiography of the aortoiliac segment and peripheral runoff vessels. We calculated the diagnostic accuracy of the duplex waveform for detecting >50% obstructive disease of the aortoiliac segment and determined the observer agreement for classifying the duplex waveforms done by two independent observers.

Results: Magnetic resonance angiography showed obstruction in 152 (39.9%) of 381 aortoiliac segments in 191 patients. The presence of a poor monophasic waveform, encountered in 91 (24.3%) of 375 segments, was a reliable sign of significant aortoiliac disease, with a positive predictive value of 92%. Other waveforms were nondiagnostic for aortoiliac obstructive disease. The sharp monophasic waveform reliably predicted occlusive disease of the superficial femoral artery that was seen in 17 of 23 instances. There was good observer agreement for classifying duplex waveforms (κ_w=0.85; 95% confidence interval, 0.80 to 0.89).

Conclusion: The poor monophasic duplex waveform at the common femoral artery is in itself an accurate marker of aortoiliac obstructive disease. Other waveforms are nondiagnostic for aortoiliac disease.

INTRODUCTION

Various noninvasive imaging modalities are in current use for the diagnostic workup of patients suspected of having peripheral arterial disease. These studies include magnetic resonance angiography (MRA), computed tomography angiography (CTA), and duplex ultrasound (DUS) scans. Although MRA and CTA are increasingly used for noninvasive vascular imaging, DUS has proved to be cost-effective and accurate for the detection of significant vascular stenoses and is therefore often used as the first diagnostic modality.[1-4] Problems may arise, however, when evaluating the aortoiliac arteries that cannot be visualized in their entirety in the 5% to 25% of patients who are extremely obese, have abundant intestinal gas, or who have particularly tortuous or calcified iliac arteries.[5,6]

It would be attractive if one could rapidly evaluate the aortoiliac arteries for the presence of significant obstructive disease without having to visualize these arteries along their entire length. This would reduce the number of indeterminate results of DUS scans, reduce the examination time for a complete DUS examination, and might also reduce the existing moderate observer variability (κ = 0.43 to 0.53) when the aortoiliac segment is evaluated.[7]

Potentially, such a rapid evaluation of the aortoiliac arteries might be provided by assessing the duplex waveform as measured distally at the level of the common femoral arteries (CFAs).[8-11] It is known that the waveform distal to a significant obstruction often changes in character, for example, from a normal triphasic waveform proximal to a stenosis to a monophasic waveform distal to the stenosis. However, only few data in the literature have addressed the question of how accurate a marker of the femoral artery DUS waveform is to show or exclude significant aorto-iliac obstruction .

The aim of the present study was, therefore, to evaluate the accuracy, predictive value, and observer agreement of the DUS waveform at the CFA as a marker of significant aortoiliac disease in a large group of consecutive patients who had a diagnostic workup for peripheral arterial disease in a vascular unit.

METHODS

Study design and patients

From October 2001 until March 2004, 250 consecutive patients who had an anklebrachial index (ABI) 0.9 at rest or a decrease in ABI of 30% after exercise were referred to the noninvasive vascular laboratory of a large community hospital by our vascular surgeons for screening of peripheral arterial disease. Of these, 234 patients had both a full DUS examination and MRA of the aortoiliac segment and peripheral runoff and formed the population of the current study. For the purpose of another, unrelated clinical trial in our institution, these patients were to undergo both examinations irrespective of the DUS or MRA results. The study we refer to is a therapeutic trial comparing exercise training with percutaneous transluminal angioplasty. Patients gave written informed consent to be part of this study and for their study data to be reported in the literature for the purpose of scientific articles.

MRA has been validated with angiography in our institution in an earlier stage. This resulted in acceptable disagreement (10%) between the two methods, and therefore, we decided to use the MRA as the reference standard. Our results were in agreement with existing data in the literature on MRA accuracy. In a meta-analysis of the literature published in 2000, the pooled sensitivity of the MRA was 97.5%, and the pooled specificity was 96.2% relative to digital subtraction angiography.[4]

We did not perform MRA in 16 patients because of recognized contraindications such as the presence of a pacemaker or claustrophobia. In all patients, DUS examinations and MRA were performed within a 4-week period.

Of the 234 eligible patients, 43 were excluded from analysis because the hard-copy prints of the DUS scan (n=16) or of MRA (n=13) were not available or because the MRA was classified as nondiagnostic due to imaging artifacts of metallic vascular stents (n=14). Therefore, in this retrospective analysis, we compared the results of DUS waveforms obtained at the CFAs of 191 patients (381 limbs), with the results of full aortoiliac MRA as the gold standard. There were 106 men (55.5%). The mean patient age was ± 67 ± 12 years (range, 34 to 96). The severity of ischemic disease according to the Fontaine classification, the vascular risk factors, and relevant comorbidity of the patients are summarized in Table I.

Table 1: Patient Characteristics and Severity of Ischemic Disease

Characteristic	n = 191	(%)
Age (y)*	67 +/- 12 (34-96)	
Male Sex	106	55.5
Hyperlipidemia	38	19.9
Cardiac disease	15	7.9
Smoking	110	57.6
Hypertension	46	24.2
Diabetes mellitus	51	26.7
Ankle Brachial Index in rest*	0.70 +/- 0.22	
Ankle Brachial Index post exercise*	0.55 +/- 0.36	
Fontaine classification:		
I: asymptomatic	0	0
II: claudication	111	58.1
III: Ischemic restpain	77	40.3
IV: Tissue loss	3	1.6

Note.
- Data are numbers of patients and percentages
* Mean age +- SD, range in parentheses

Duplex ultrasound scans

Color duplex examinations were performed at the CFA with a 5-MHz transducer (Aloka SSD-2000, Aloka, Tokyo, Japan) by one of three registered vascular technologists according to a standardized routine examination protocol in our institution.

Duplex waveforms were obtained 10 to 20 mm proximal to the femoral bifurcation at the location where color change suggested the highest velocity. Care was taken to obtain DUS measurements at 60° Doppler insonation angles. The patients made one visit to the vascular laboratory in which the duplex waveform of the CFA was recorded on a video print and archived in the patients' records.

For the purpose of this study, the video prints of the DUS waveforms were retrieved, anonymized, and presented to two independent vascular technologists (K.G., W.D.) who were blinded to the patient's identity, clinical findings, and the results of the MRA. The left and right CFA waveforms in a given patient were treated as two separate examinations. The duplex waveform was classified into one of four categories:[12]

1. *Triphasic:* three waveform "phases" consisting of a sharp systolic forward up rise and fall, an element of reverse flow during diastole, and an element of forward flow during diastole (Fig 1).
2. *Biphasic:* two waveform "phases" consisting of a sharp systolic forward up rise and fall and an element of reverse flow during diastole (Fig 2).
3. *Sharp monophasic:* one waveform "phase" with a sharp systolic rise, the lack of a reverse diastolic element, and a fast diastolic fall, expected in arterial segments proximal to an obstruction (Fig 3).
4. *Poor (blunted) monophasic:* the loss of "sharpness" in systole, the lack of a reverse diastolic element, and a slow diastolic fall expected in arterial segments distal to an obstruction (Fig 4).

Magnetic resonance angiograms

MRAs were obtained on a 1.5T MR system unit and by using dedicated MR hardware for peripheral MRA (Gyroscan Intera 1.5 TN; MobiTrak; Philips Medical Systems, Best, The Netherlands). A T1 weighted three-dimensional gadolinium-enhanced gradient echo sequence was employed with transverse time-of-flight scout views and by using the system's array body coil. Parameters were repetition time, 5.9 ms; echo time, 1.62 ms; flip angle, 35°; and slice thickness, 1.5 mm. Acquisition times were between 1.31 minutes and 2.37 minutes. MRAs of the aortoiliac segment and the lower limbs were obtained in 26 seconds with a 75% rectangular field of view of 450 * 315 mm and a matrix of 512 * 512. This resulted in a voxel size of 0.80 3.05 1.5 mm^3 before interpolation. The calculated voxel size after interpolation was 0.80 * 1.5 * 1.5 mm^3.

Forty ml of gadolinium diethylenetriaminepentaacetic (DTPA) acid contrast material were infused at a rate of 2 ml/second using a power injector. Maximum intensity projections in multiple projections and source images were stored on hard copy. For analysis, the hard-copy films were retrieved and independently read by two experienced radiologists who were blinded to the results of the DUS examinations and to the clinical information (P.M.T.P., L.C.W.J).

The arterial tree was divided in the following segments for analysis: the aortoiliac segments, consisting of the distal aorta, the common iliac artery, and the external iliac artery; and the more distal segments, consisting of the CFA, the superficial femoral artery (SFA), and the popliteal artery. The segments were scored as either normal or as obstructed whenever a 50% diameter stenosis was present. The most severe stenosis in each segment was chosen for classification. Each limb consisted of the aortoiliac segments and the more distal segments.

Any resulting disagreements between the two readers were resolved by a third independent reader (L.v.D, an experienced radiologist) who was blinded to the results of the DUS scan, clinical information, and the specific readings of the two other radiologists. The final MR results were taken as the gold standard in the evaluation of this study.

Figure 1: Triphasic: three waveform 'phases'; a sharp systollic forward up rise and fall, an element of reverse flow during diastole, and an element of forward flow during diastole.

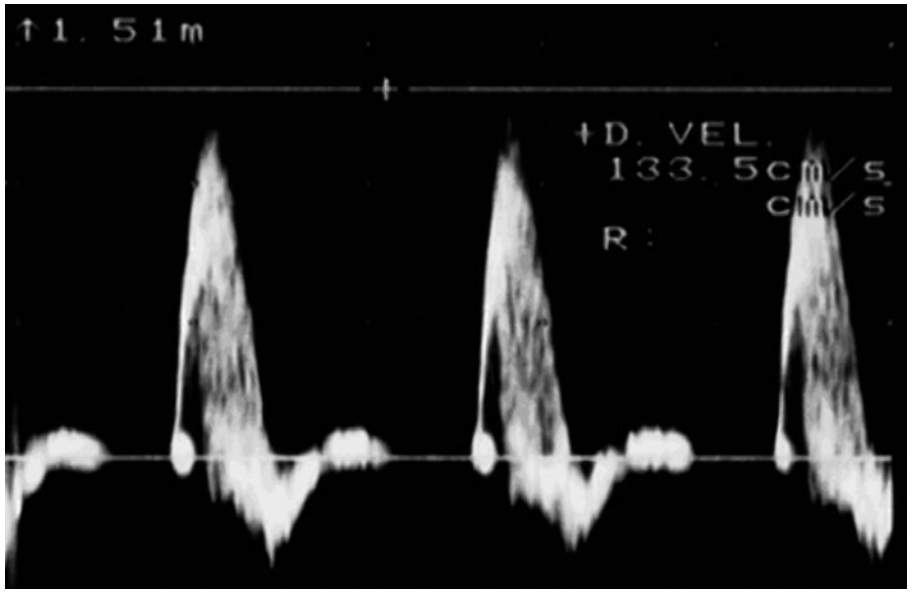


Figure 2: Biphasic: two waveform 'phases'; a sharp systolic forward up rise and fall, and an element of reverse flow during diastole.

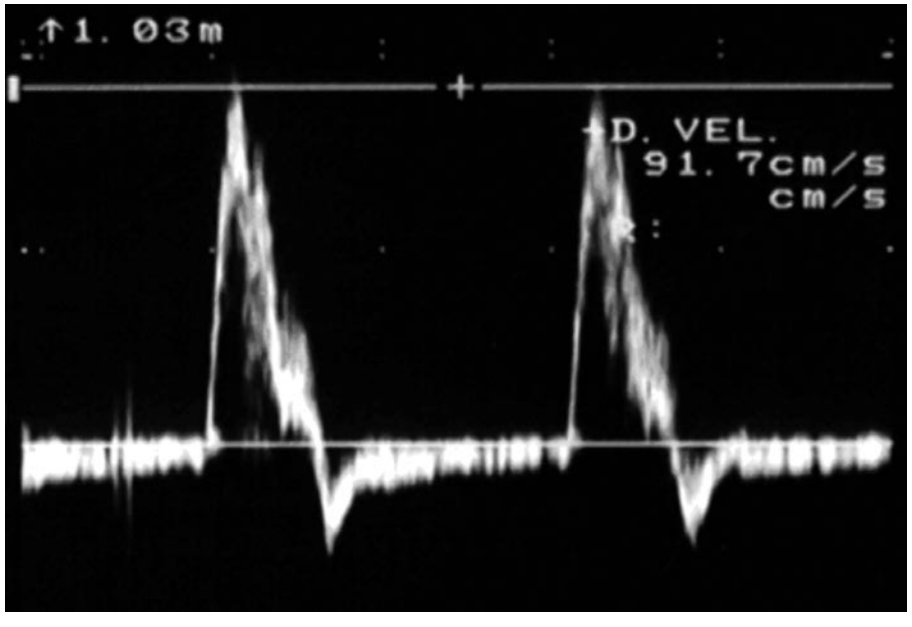


Figure 3: Sharp monophasic: a sharp systolic rise, the lack of a reverse diastolic element, and a fast diastolic fall.

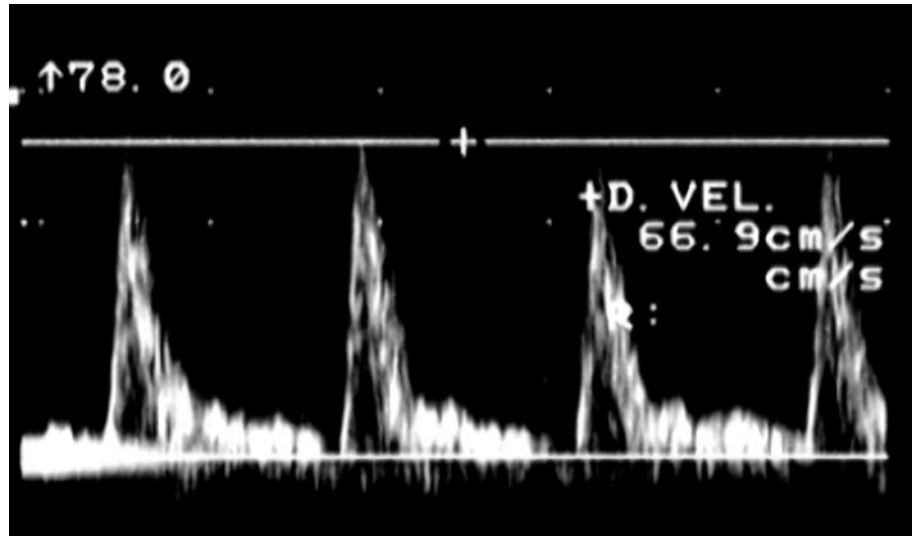
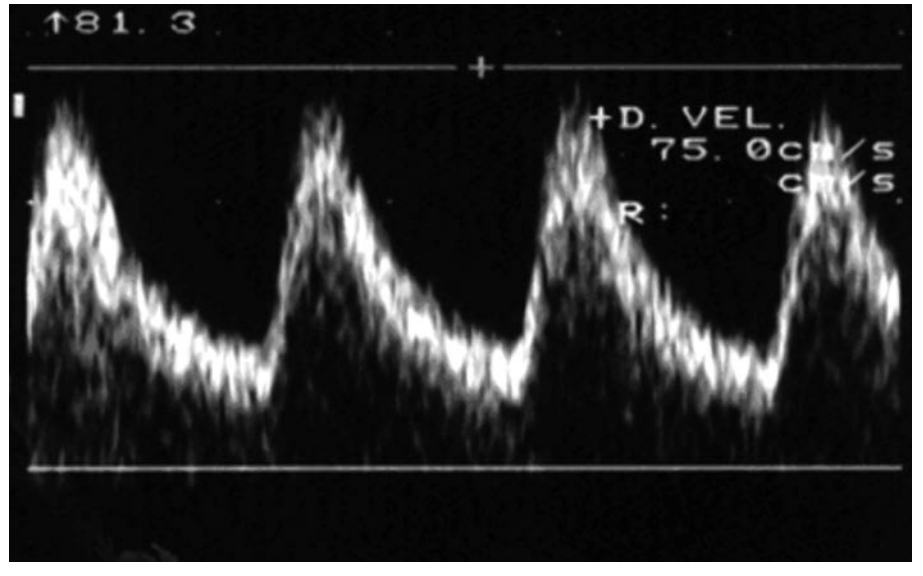


Figure 4: Poor monophasic: the loss of "sharpness" in systole, the lack of a reverse diastolic element, and a slow diastolic fall.



Statistical analysis.
Two-way contingency tables were made comparing the duplex waveform at the CFA versus the presence of significant obstructive disease in the corresponding aortoiliac segment on MRA. The accuracy, sensitivity, specificity, and positive predictive value as well as the negative predictive value of the duplex waveform for detecting 50% obstructive disease of the aortoiliac segment was calculated separately for the two DUS scan readers.

The analysis was done three times. In the first analysis, all triphasic and sharp monophasic waveforms (expected in arterial segments proximal to an obstruction) were grouped together as "normal," and all biphasic and poor monophasic waveforms were regarded as "abnormal." In the second analysis, triphasic, biphasic, and sharp monophasic waveforms were regarded as normal. Finally, the duplex waveforms were grouped as in the second analysis but this time for comparing the presence of aortoiliac stenotic disease versus the presence of total occlusive disease in the corresponding aortoiliac segment on MRA. Separate analyses were performed to adjust for the potential confounding effects of downstream disease1[3-15] and also for the effect of disease severity (claudication vs critical ischemia).

The weighted kappa statistic (κ_w) was used to test for observer agreement for assessing the duplex waveform. If duplex waveform prints were classified as nondiagnostic by one of the two DUS readers, the classified duplex waveform was used for the analyses. Calculations were performed with the Statistical Package for the Social Sciences (SPSS) software release 11.0.1 (SPSS, Chicago, Ill) for Windows (Microsoft, Bellingham, Wash) and the Statistical Analysis System (SAS) 8.2 software (SAS Institute Inc., Cary, NC) for Windows (Microsoft).

RESULTS

The MRAs showed that 152 (39.9%) of 381 aortoiliac segments in 191 patients had obstruction, in particular, 50% stenosis in 125 and occlusion in 27 segments, three of which were aortic occlusions. Downstream disease due to significant SFA obstruction was present in 221 (58%) of 381 SFA segments (i.e., 50% stenosis in 141 and occlusion in 80 segments), whereas significant popliteal artery obstruction was present in 74 (19.4%) of 381 limbs (i.e. 50% stenosis in 50 and occlusion in 24 segments). Disagreements between the two MRA readers were found in the aorta (4%), iliac segment (14%), SFA segment (9%), and popliteal segment (8%) and were resolved by the third independent reader.

Duplex ultrasound scans.
A total of 6 (1.6%) of 381 duplex waveforms prints were classified as nondiagnostic by both DUS readers and were excluded from analysis. The interobserver agreement for assessing the duplex waveform characteristics at the CFA of the remaining 375 limbs was very high (Kw 0.85; 95% CI, 0.80 to 0.89). A total of 28 (7.3%) duplex waveform prints were classified nondiagnostic by one of the two DUS readers due to CFA occlusive disease, aortobifemoral bypass graft, femoral artery patch, or because of artifacts on the prints.

The interobserver agreement for assessing the monophasic waveform was also very high (κ_w = 0.92; 95% CI, 0.88 to 0.97), whereas by differentiating between the sharp monophasic waveform and the poor monophasic waveform, the interobserver agreement was still high (κ_w = 0.80; 95% CI, 0.68 to 0.92).

Analysis.
The results of the four duplex waveform categories compared with the MRA findings are summarized in Table II for DUS reader 1. The values for reader 2 were similar, attesting to the very high interobserver agreement, and are not separately shown. It can be immediately seen from Table 2 that the presence of a "normal" triphasic duplex waveform at the CFA did not exclude significant obstructive aortoiliac disease, which was present in 51 (24.6%) of 207 segments. By contrast, a poor monophasic waveform was closely correlated with aortoiliac disease, with high positive predictive value of 92% (84 of 91 aortoiliac segments).

Table 2: Duplex waveforms at the common femoral artery versus the presence of significant aortoiliac obstruction

CFA duplex waveform	No aortoiliac obstruction	Aortoiliac obstruction present*	Total
Triphasic	156	51	207
Biphasic	42	12	54
Sharp monophasic	19	4	23
Poor monophasic	7	84	91
Nondiagnostic	5	1	6
Total	229	152	381

CFA, Common femoral artery.
*Defined as 50% diameter stenosis or occlusion as seen on contrastenhanced magnetic resonance angiography.

Thus the most useful analysis was to group triphasic, biphasic, and sharp monophasic waveforms together as "normal" and the poor monophasic waveform as "abnormal." This classification had high specificity (97%) and positive predictive value (92%), but low sensitivity (56%) and negative predictive value (80%) (Table 3). Thus, only the poor monophasic waveform had diagnostic importance, and whenever it was encountered, it reliably identified aortoiliac disease.

More specific diagnosis of stenotic versus occlusive aortoiliac disease proved not feasible by using the duplex waveform. The poor monophasic waveform was associated with occlusive disease in 31 and with stenotic obstruction in 53. It is of note that triphasic and biphasic waveforms were seen in 3 of 34 and 0 of 34 aortoiliac occlusions, respectively. As an additional finding, it was of interest that the sharp monophasic duplex waveform at the CFA was associated with occlusion of the superficial femoral artery (11 total occlusions and 6 segmental occlusions) in 17 (73.9%) of 23 instances.

Once the waveforms were grouped as in the second analysis (only the poor monophasic waveform grouped as abnormal), further subanalysis showed differences between 74% and 50% sensitivity and between 65% and 88% specificity. Although the differences are fairly large, we could not demonstrate a significant difference, probably because of the small number of patients in the subgroup. In addition, no significant difference could be demonstrated in predicting aortoiliac disease between patients with claudication versus those with critical ischemia (sensitivity, 57% vs 56% and specificity, 87% vs 86%)

Table 3: Duplex waveforms at the common femoral artery versus the presence of significant aortoiliac obstruction*

CFA duplex waveform	No aortoiliac obstruction	Aortoiliac obstruction present†	Total
Triphasic, biphasic, and sharp monophasic grouped together.	217	67	284
Poor monophasic	7	84	91
Total	224	151	375
	(%)	95% confidence interval	
		Lower	Upper
Sensitivity	56	48	63
Specificity	97	94	98
Positive predictive value	92	85	96
Negative predictive value	76	71	81
Accuracy	80	76	84

CFA, Common femoral artery.
*Analysis 2 (see text). The poor monophasic duplex waveform classified as "abnormal", all other waveforms grouped together as "normal".
†Defined as 50% diameter stenosis or occlusion as seen on contrastenhanced magnetic resonance angiography.

DISCUSSION

Duplex imaging of the CFA is an easily performed test with high observer agreement for classification of the duplex waveform. The current study shows that such classification has diagnostic value in those patients in whom a poor monophasic waveform is present. In our study, we saw this waveform in approximately one quarter of patients. The presence of the poor monophasic waveform accurately identifies obstructive disease in the proximal aortoiliac vessel segments with positive predictive value of 92%. The other duplex waveforms have no diagnostic value for predicting the status of the proximal vessels: even a "normal" triphasic waveform is seen in almost a quarter of patients with aortoiliac obstruction or occlusion.

For clinical decision making, the relevant issue is if a hemodynamically significant stenosis is present; and usually, 50% diameter stenosis is implied as meaning it is. In addition, it is of interest if this is stenotic disease or complete occlusion. We have designed the scoring sheets of the reference standard accordingly.

Although one would expect the poor waveform in the CFA with an occlusion, as we report here, we encountered some patients who had occlusion but a biphasic or triphasic CFA waveform. Also, our findings demonstrated that a more specific diagnosis of stenotic versus occlusive aortoiliac disease was not possible by using the duplex waveform. A more accurate grading would be therefore not feasible. Occurrence of the sharp monophasic waveform has value in a way that it marks occlusion of the SFA. Knowledge of these flow characteristics may also be helpful in reducing DUS examination time or in arriving at a correct diagnosis whenever the iliac arteries cannot be visualized in their entirety.

Our diagnostic algorithm is first to check the CFA waveforms and then to proceed with trying to see the aortoiliac arteries in their entirety. The value of the current results in our practice is that we can be confident that a hemodynamically significant stenosis is present when we measure a poor CFA waveform, even if we do not succeed in visualizing the ipsilateral iliac artery. One might also argue that once a poor CFA waveform is encountered, this patient will need to undergo a more definitive imaging study and the duplex examination can be considered completed. This would be time consuming. Our study specifically warns that this shortcut cannot be taken too far: one cannot exclude the presence of hemodynamically significant disease in the aortoiliac arteries from a triphasic or biphasic CFA waveform.

A previous study compared the duplex waveform interpretation against aortoiliac duplex scanning and found sensitivity and specificity of 95% and 80%.[10] Unfortunately, it is not clearly stated in this study if the second duplex waveform observer also did the assessment of the full DUS. Otherwise, it could have created observer bias and could also clarify the lower observer agreement between the two duplex waveform observers (κ= 0.74). Another study validated the systolic rise time of the Doppler waveform by correlation with angiograms; however for this study, a group of patients with SFA obstruction was selected.[16]

A more recent study compared the interpretation of the CFA against aortoiliac disease by using arteriography as the gold standard and found sensitivity and specificity of 95% and 89%.8 It must be noted that in this study, 31% of the significant aortoiliac diseases contained occlusive disease, which is more likely to be detected, whereas this was 18% in our study. We found a substantially lower sensitivity, which implies that a normal duplex waveform cannot exclude significant aortoiliac disease. However, the lower sensitivity is not surprising, because it has previously been described that a duplex waveform recorded at a sufficient distance from a stenosis can normalize.[10,17]

Some limitations of our study should be discussed. A known limitation of MRA findings is that overestimation of stenosis grade is more frequent than underestimation.[18] This might explain some of the false-negative DUS interpretations, but given the sheer amount of false-negative results found here, it would not affect the overall conclusions of the present study. Furthermore, we are aware of the 18% MRA disagreement in the aortoiliac segments and made our reference standard more reliable by requiring a third MRA reader. When we performed a subanalyses for the two different MRA readers versus the duplex results separately, the conclusions were robust, in that these were similar to the conclusions of our study reported here.

Another limitation of this study may be that the waveform interpretations were made directly from the prints and not from real-time DUS scans. Some prints that both DUS readers classified as nondiagnostic because of artifacts might have been assessable in a real-time DUS scan, and this could have caused false noninterpretable waveforms in the study.

CONCLUSIONS

The observer agreement in assessing the DUS waveform at the CFA is very high. The poor monophasic duplex waveform at the CFA is in itself an accurate marker of upstream aortoiliac obstructive disease. The appearance of triphasic and biphasic monophasic waveforms is nondiagnostic for aortoiliac disease, whereas the sharp monophasic duplex waveform is associated with occlusion of the superficial femoral artery.

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9 SUMMARY

SUMMARY

The studies presented in this thesis all focus on management of patients with intermittent claudication. They cover a broad spectrum and include the impact of intermittent claudication on health-related quality of life, the evaluation of the outcomes of endovascular revascularization compared to supervised hospital-based exercise training, the evaluation of new rehabilitation strategies for coronary artery disease, and the evaluation of a diagnostic test for aorto-iliac arterial disease.

The shortcomings and merits of the individual studies presented have been discussed in the previous chapters. In this chapter, a summary of the main findings is presented. Subsequently, some methodological issues are discussed and implications for future research are considered.

Intermittent claudication is the first and mildest manifestation of peripheral arterial disease, caused by the atherosclerotic process of progressive narrowing of arteries. Intermittent claudication is the clinical condition of lower extremity muscle pain, discomfort, or weakness in the lower extremity induced by exercise and relieved by short periods of rest. The symptoms are explained by impaired blood flow to the lower extremity and are caused by partial or complete narrowing of one or more of the arteries of the peripheral circulation. If the arterial system fails, it results in a progressive oxygen debt, experienced by the patient as cramping muscle pain.

The general consensus is that all patients presenting with intermittent claudication should initially be treated with exercise training and only if symptoms fail to improve, should invasive procedures be considered. Endovascular revascularization, however, may provide immediate benefit and therefore may prevent a patient's 'unnecessary disability'. This has led to new controversy as to the role of endovascular revascularization compared to exercise training in patients with intermittent claudication. This is accompanied by an ongoing debate about the costs of the optimal treatment for patients with intermittent claudication. We compared the clinical effectiveness and cost-effectiveness of endovascular revascularization to hospital-based exercise training in patients with intermittent claudication at 6- and 12 –month's follow-up. In **Chapter 1** a broader rationale for this research project is presented.

Improvement in health-related quality of life is the ultimate goal of healthcare for the treatment of intermittent claudication. Until recently, the measures of success after treatment were those derived from the vascular laboratory, including ankle-brachial indices and ankle and toe pressures. There are now several validated and reliable survey instruments that can assess patient-reported health-related quality of life in a generic or disease-specific manner. Major survey instruments are reviewed. Although intermittent claudication is neither life- nor limb threatening, it has a significant negative impact on health-related quality of life, as measured by these instruments. Patients so afflicted report more bodily pain, worse physical functioning, and worse perceived health, in addition to limited walking ability. In general, these measures of health-related quality of life do not correlate with standard parameters of ankle-brachial index or ankle pressures. Therefore, the information gathered through these health-related quality-of-life assessment tools is important to all those involved in the management of patients with intermittent claudication.

Treatment of the claudicant with exercise training and percutaneous or open revascularization impacts health-related quality of life as well. Each of these treatment modalities is capable of improving health-related quality of life, but some are associated with recurrent symptoms over time. The major benefits and risks to health-related quality of life of these specific forms of treatment for the claudicant are reviewed. In **Chapter 2** we demonstrated that patients who suffer from symptoms of intermittent claudication are best served by management that addresses their major self-reported impediments to health-related quality of life.

To evaluate the effects after endovascular revascularization versus exercise training in patients with intermittent claudication, a systematic review was performed (**Chapter 3**). Articles published between 1980 and February 2003 were included if patients with intermittent claudication were treated with (a) exercise training, or (b) angioplasty, and (c) both functional capacity and the SF-36 quality-of-life scores were reported of at least 3 months follow-up. Data were pooled using the random-effects model and weighted means. Pooled results were compared between the treatment groups using the χ^2-test, and the t-test ($\alpha = 0.05$, two-sided). In the analyses, 5 studies (n=202 patients) were included in the exercise group and 3 studies (n=470 patients) in the angioplasty group.

Comparison of published results of exercise training with published results of endovascular revascularization demonstrated an improvement in health-related quality of life after exercise training at 3 and 6 months, whereas after endovascular revascularization both functional capacity and health-related quality of life showed significant improvement at 3 and 6 months. Between the two treatment groups the ankle-brachial indices were significantly higher in the endovascular revascularization group compared to the exercise training group at 3 and 6 months, whereas the improvement in health-related quality-of-life scores was not significantly different between the treatment groups during follow-up.

In the systematic review, the lack of standardization in the different protocols of exercise training became apparent. This hampered the comparison of the reported results between the treatment options. Therefore, a prospective randomized controlled trial was performed (**Chapter 4** and **5**) to compare the clinical effectiveness and cost-effectiveness of endovascular revascularization to supervised exercise training. From September 2002 to September 2005 all consecutive new patients with signs and symptoms of intermittent claudication, who were referred to a Vascular Surgery Department, were potentially eligible for recruitment. Of 293 potentially eligible patients with symptoms of intermittent claudication due to an iliac or femoro-popliteal arterial lesion, 151 fulfilled the inclusion criteria and were randomly assigned to endovascular revascularization (76 patients) or supervised hospital-based exercise training (75 patients).

In **Chapter 4** we described the clinical effectiveness of this randomized controlled trial. The outcome measures included clinical success, functional capacity, and health-related quality of life after 6 and 12 months. Significance of differences between the groups was assessed with the unpaired t-tests, χ^2-test or the Mann-Whitney U-test. To adjust outcomes for imbalances of baseline values we performed multivariable regression analysis.

Endovascular revascularization yielded a larger improvement compared to supervised hospital-based exercise in clinical success immediately after the start of treatment, but this advantage was lost after 6 and 12 months (OR 1.2; 95% CI 0.5, 2.5, p=0.70 and OR 0.9; 95% CI 0.4, 1.7, p=0.73 respectively). After endovascular revascularization there were significantly fewer patients with ipsilateral symptoms compared to supervised exercise at 6 months (37% vs. 69%; OR 0.4; 95% CI 0.2, 0.7, p<0.001) but no significant differences were demonstrated at 12 months. After both treatments, there was an increase in functional capacity and quality-of-life scores after 6 and 12 months, with a statistical significant dif-

ference between the treatment groups only in the maximum pain-free walking distance in favour of the supervised hospital-based exercise group after 6 months (mean difference 16 meters; 95% CI 2, 29 meters, p=0.02). All other outcomes and all outcomes at 12 months demonstrated no significant differences.

The results demonstrated that patients with intermittent claudication benefited from both endovascular revascularization and supervised hospital-based exercise. Initially minor differences in outcomes between the two treatments may occur but at 12 months no significant differences can be demonstrated.

In **Chapter 5** we described the cost-effectiveness of this randomized controlled trial. The primary outcome was health-related quality of life (EuroQol, rating scale, SF36, quality-adjusted life years accumulated during 12 months) and the secondary outcome was costs from the societal perspective. Significance of differences between the groups was assessed with the unpaired t-test, χ^2-squared-test, and the Mann-Whitney U-test. Incremental costs per quality-adjusted life year gained were calculated as the difference in total mean cumulative costs during 12 months between the treatment groups divided by the difference in mean accumulated quality-adjusted life years during 12 months. Outcomes were adjusted for baseline quality-of-life values and covariates using multivariable regression analysis.

The endovascular revascularization group had a larger improvement in 6- and 12-months EuroQol, rating scale, and SF-36 quality-of-life values than the supervised hospital-based exercise, but the differences were not statistically significant. The gain in total mean QALYs accumulated during 12 months, adjusted for baseline values, was significantly larger following endovascular revascularization (mean difference 0.03; 95% CI: 0.02, 0.04; p<0.001). The total mean cumulative costs per patient were significantly higher in the endovascular revascularization group (mean difference €2318; 95% CI: €2176, €2460; p<0.001) and the incremental cost per QALY was €77 267.

Endovascular revascularization results in a small gain in effectiveness compared to supervised hospital-based exercise during 12-months' follow-up but costs more, and only if society is willing-to-pay more than 77 300 €/QALY gained should one consider endovascular revascularization as first-line treatment in patients with intermittent claudication.

Chapter 6 and **7** deal with the management of patients with both peripheral arterial disease and coronary artery disease. These patients frequently fail the cardiac rehabilitation program due to their limited walking distance. The purpose of the study described in **Chapter 6** was to evaluate whether clinical effectiveness of cardiac rehabilitation is related to the presence of peripheral arterial disease. From a consecutive cohort of patients who started cardiac rehabilitation from January 2004 to December 2004, we included those who completed the Walking Impairment Questionnaire (n=126). Cardiac rehabilitation failure was defined as a premature discontinuation of the treadmill exercise program or an inability to reach target heart rate. Presence of peripheral arterial disease was based on the walking distance score and the speed score of the Walking Impairment Questionnaire and in a subset of our patient sample (n=39) we assessed the ankle-brachial index (ABI). Chi-squared tests were used to compare the proportion of patients with peripheral arterial disease between patients who failed cardiac rehabilitation and patients who were successful. In addition, age and sex adjusted logistic regression models were used to examine the association between cardiac rehabilitation failure and the presence of peripheral arterial disease.

The presence of peripheral arterial disease based on the walking distance score of the Walking Impairment Questionnaire was significantly higher in the cardiac rehabilitation failure group than in the success group (34% vs. 17%, OR 2.5; 95% CI 1.1 to 6.0, p=0.03). The presence of peripheral arterial disease based on the walking speed score of the Walking Impairment Questionnaire, however, was not significantly different (30% vs. 28%, OR 1.1; 95% CI 0.5 to 2.5, p=0.79). The presence of peripheral arterial disease based on ABI measurements was higher in the failure group than in the success group (39% vs.14%, OR 3.8; 95% CI 0.8 to 17.9, p=0.08). Logistic regression analysis showed that when cardiac rehabilitation failure was adjusted for age and sex, failure was significantly associated with the presence of peripheral arterial disease based on the walking distance (OR 2.8; 95% CI 1.1 to 7.1, p=0.03), but not significantly associated when based on the speed score (OR 1.2; 95% CI 0.5 to 2.8, p=0.72).

This study demonstrated that the clinical effectiveness of cardiac rehabilitation was inversely related to the presence of peripheral arterial disease, which suggests that patients with peripheral arterial disease benefit less from a cardiac rehabilitation program and are at higher risk of future cardiac events.

In order to improve the results of current cardiac rehabilitation, we evaluated the cost-effectiveness of new rehabilitation strategies in which diagnosis and treatment of peripheral arterial disease in coronary artery disease patients were considered (**Chapter 7**). An analytic Markov decision model was developed to determine the optimal rehabilitation strategy for patients with peripheral arterial disease in coronary artery disease patients undergoing cardiac rehabilitation.

The Markov decision model compared the following treatment strategies: 1. Cardiac rehabilitation (current practice); 2. Diagnostic work-up if cardiac rehabilitation fails followed by revascularization for peripheral arterial disease if needed; 3. Diagnostic work-up for peripheral arterial disease in all patients prior to cardiac rehabilitation and revascularization for peripheral arterial disease if needed; 4. A hypothetical comprehensive combined cardiovascular rehabilitation program. The best-available evidence was retrieved from the literature and combined with primary data from 231 patients. Quality-adjusted-life years (QALYs), lifetime costs, incremental cost-effectiveness ratios (ICER), and the gain in net health benefits (NHB) were calculated.

The hypothetical comprehensive cardiovascular rehabilitation program was the most attractive with an ICER of $16,461 per QALY gained and a gain in NHB of 0.06 compared to current practice. In an analysis without this strategy, a diagnostic work-up if cardiac rehabilitation fails followed by revascularization for peripheral arterial disease if needed was most beneficial with an ICER of $49,468 per QALY gained and a gain in NHB of 0.02 compared to current practice.

A combined cardiovascular rehabilitation program, or a diagnostic work-up and revascularization for peripheral arterial disease in patients who fail cardiac rehabilitation, would decrease secondary cardiac events and save society millions of dollars.

In **Chapter 8** a diagnostic test evaluation is described. Duplex ultrasound is often used to plan the treatment strategy for patients with peripheral arterial disease. However, Duplex Ultrasound is operator-dependent and does not provide a "roadmap" of the arterial system. The accuracy, predictive value and observer agreement of the duplex ultrasound waveform at the common femoral artery as a marker of significant aorto-iliac disease was assessed. In 191 consecutive patients (381 aorto-iliac segments) who visited the vascular laboratory between October 2001 and March 2004, we classified the duplex ultrasound waveform at the common femoral artery as triphasic, biphasic, sharp mono-

phasic, or stump monophasic. The waveforms were then compared with the findings of magnetic resonance angiography of the aorto-iliac segment and peripheral run-off vessels. We calculated the diagnostic accuracy of the duplex waveform for detecting >50% obstructive disease of the aorto-iliac segment and determined the observer agreement for classifying the duplex waveforms done by two independent observers.

The presence of a stump monophasic waveform, encountered in 91/375 segments (24.3%), was a reliable sign of significant aorto-iliac disease with a positive predictive value of 92%. Other waveforms were non-diagnostic for aorto-iliac obstructive disease. The sharp monophasic waveform reliably predicted occlusive disease of the superficial femoral artery, seen in 17/23 instances. There was good observer agreement for classifying duplex waveforms (κ_w = 0.85; 95% CI, 0.80 to 0.89). Our results suggested that the stump monophasic duplex waveform at the common femoral artery is in itself an accurate marker of aorto-iliac obstructive disease. Other waveforms are nondiagnostic for aorto-iliac disease.

METHODOLOGICAL CONSIDERATIONS

Several study designs were used to address the clinical problem, each with its own merits and limitations. A systematic review was used to summarize the available evidence of the results of endovascular revascularization and exercise training after 6 months' follow-up. The aims of a systematic review are to collect all available evidence, to integrate the results of independent studies that on their own may have contradictory or non-significant results, and to increase power so that an overall conclusion can be made. By doing the systematic review, however, we found that the exercise training protocols were not uniformly performed across the studies, which hampered comparison.

Another study design that we used was the randomized controlled trial (RCT). RCT's minimize bias introduced by extraneous factors and ensure an unbiased comparison between treatment groups. Patients were randomized after obtaining informed consent and prior to the initial treatment, which is the most straightforward practical approach. In general, RCT's may not always be the most efficient approach because they are time-consuming and can be expensive, but we found our randomized controlled trial to be both feasible and inexpensive.

A third study design we used was a cohort study for a clinical study in which we evaluated whether clinical effectiveness of cardiac rehabilitation was related to the presence of peripheral arterial disease. We found an association between cardiac rehabilitation failure and the presence of peripheral arterial disease but, as with all cohort studies, an association does not automatically imply a cause-effect relationship.

A fourth study design was a decision-analytic model in which we compared different rehabilitation strategies for patients with coronary artery disease. The goal of performing a decision analysis is to integrate the best-available evidence in a model that reflects reality but since reality is complex, assumptions have to be made to keep the model manageable. In addition, the input variables of decision models come from various sources, each with potential confounding factors. However, advantages of decision models are that many alternative strategies can be compared and that lifetime outcomes can be estimated which cannot be done in a clinical study for ethical and practical reasons. Another advantage of decision models is that "what if" (sensitivity) analyses can be performed to explore the uncertainty of the input variables. Probabilistic sensitivity analysis is particularly useful in this respect. Finally, value of information analysis can be performed to estimate the value of obtaining further information through future research.

Another cohort study design was used for the diagnostic test evaluation of duplex ultrasound, which focused on determining sensitivity and specificity of the duplex ultrasound in comparison to a reference test. Reference tests are, however, commonly not as perfect as we would like them to be. In our cohort study this problem applied to magnetic resonance angiography. As known from previous studies, overestimation of stenosis grade with magnetic resonance angiography is more frequent than underestimation. This may have caused some false negative duplex ultrasound interpretations.

FUTURE DIRECTIONS

Many clinical and methodological issues need further research, of which most were presented in the previous chapters. The studies presented in this thesis all focused on management of patients with intermittent claudication. Regardless of the initial treatment, claudicants should be encouraged to engage in regular exercise and atherosclerotic risk factors need ongoing attention during the follow-up period. Endovascular revascularization plus supervised exercise training or endovascular revascularization plus pharmacologic therapy are comprehensive management strategies that should be considered in future research.

The studies presented in this thesis were based on the techniques available at the time the studies were conducted. New developments in endovascular revascularization technology for peripheral arterial disease are bare-metal, drug-eluting, and covered stents. These techniques are under development and broaden the type of lesions and disease locations that can be treated. However, long-term patency data on these new technological advancements are currently not available.

The association between the presence of peripheral arterial disease and cardiac rehabilitation failure emphasizes the need to explore alternative strategies to diagnose and treat peripheral arterial disease in patients undergoing cardiac rehabilitation. Based on our value of information analysis more research on the costs and effectiveness of new rehabilitation strategies in patients with coronary artery disease is justified. The results from our study can help design a future study and restrict the data collection to the most relevant variables. This could potentially increase the success of the program and improve cardiovascular risk reduction.

A new development in duplex ultrasound for examination of the aortoiliac arteries is the use of contrast agents. These increase the Doppler signal intensity and should therefore reduce the rate of uninterpretable test results. Other future directions include ultrasound-guided therapy of arterial occlusions using encapsulated drugs targeted to the thrombus.

Clinical implications for the management of patients with intermittent claudication:

1. The results of our randomized controlled trial demonstrated a small gain in effectiveness after endovascular endovascularization compared to supervised hospital-based exercise during 12-months' follow-up, but endovascular endovascularization was also more expensive, and only if society is willing-to-pay more than 77 300 €/QALY gained should one consider endovascular revascularization as first-line treatment in patients with intermittent claudication.

2. Peripheral arterial disease can limit the benefit of cardiac rehabilitation in patients with coronary artery disease. A combined cardiovascular rehabilitation program, or if this is unavailable, a diagnostic work-up for PAD in patients who fail cardiac rehabilitation followed by revascularization if needed, could potentially decrease secondary cardiac events and save society millions of dollars.

SAMENVATTING

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Het onderwerp van dit proefschrift gaat over management van claudicatio intermittens tengevolge van atherosclerose in de perifere arteriën. Patiënten met claudicatio intermittens krijgen kramp in de benen bij inspanning en deze klachten verdwijnen na rust. Van deze patiënten met claudicatio intermittens wordt daarom gezegd dat ze last hebben van "etalagebenen": de patiënt loopt een stukje, rust even uit voor een etalage en kan dan weer verder lopen. De symptomen worden veroorzaakt door perifeer arterieel vaatlijden, waardoor een verminderde doorbloeding ontstaat tengevolge van vernauwingen of verstoppingen in de bloedvaten die de benen van zuurstofrijk bloed voorzien. Als behandeling komen looptraining en endovasculaire revascularisatie, beter bekend als "Dotteren" in aanmerking. Van oudsher wordt voor claudicatio intermittens een looptrainingsprogramma aanbevolen, waarbij de relatief invasieve endovasculaire revascularisatie pas wordt ingezet wanneer de looptraining heeft gefaald. Echter, door het vroege klinische succes van endovasculaire revascularisatie, de technische innovaties en de lage morbiditeit en mortaliteit, wordt de endovasculaire revascularisatie steeds vaker toegepast. Sommige behandelaars vragen zich daarom af of de looptraining nog wel gerechtvaardigd is om dat met endovasculaire revascularisatie een periode van onnodig invaliderend lijden kan worden voorkomen. Aan de andere kant spelen de kosten ook een belangrijke rol en vanuit het oogpunt van kosteneffectiviteit zou de endovasculaire revascularisatie misschien bewaard moeten worden voor meer ernstige symptomen dan claudicatio intermittens. In **Hoofdstuk 1** wordt een algemene beschouwing gegeven over dit wetenschapsproject.

Hoewel claudicatio intermittens niet meteen bedreigend is voor het been, veroorzaakt de beperkte loopafstand en de pijn tijdens het lopen voor een vermindering in de fysieke en geestelijke gesteldheid. Verbetering van kwaliteit van leven is het uiteindelijke doel bij de behandeling van claudicatio intermittens. Tot voor kort werd de mate van succes van de behandeling bepaald aan de hand van enkel-arm indexen. Tegenwoordig zijn er ook gevalideerde en betrouwbare vragenlijsten waarmee de kwaliteit van leven van de patiënt kan worden beoordeeld voor en na de behandeling. In het algemeen blijken deze maten voor kwaliteit van leven niet goed te correleren met de enkel-arm index. In **Hoofdstuk 2** gaven we een overzicht van de impact van claudicatio intermittens en de behandeling op de kwaliteit van leven. Patiënten met claudicatio intermittens rapporteerden naast de beperkte loopafstand ook een verslechterde lichamelijke functie, toegenomen lichamelijke pijn en verminderde algehele gezondheid. Ook de behandeling van claudicatio intermittens heeft invloed op de kwaliteit van leven. Hoewel looptraining en endovasculaire revascularisatie de kwaliteit van leven verbeteren, blijkt er na van loop van tijd weer een afname in kwaliteit van leven te ontstaan door terugkerende symptomen. In dit hoofdstuk demonstreerden we dat patiënten met claudicatio intermittens het beste zijn geholpen met een behandeling die is gericht op het verbeteren van de kwaliteit van leven van de patiënt.

Om een beter zicht te krijgen op de effecten van endovasculaire revascularisatie in vergelijking met looptraining hebben we een systematisch literatuur onderzoek uitgevoerd waarbij de verandering in kwaliteit van leven en functionaliteit na endovasculaire revascularisatie en looptraining zijn vergeleken (**Hoofdstuk 3**). Gepubliceerde artikelen tussen 1980 en februari 2003 werden geïncludeerd wanneer de claudicanten waren behandeld met (a) looptraining, of (b) endovasculaire behandeling en (c) zowel functionaliteit als ook de SF-36 kwaliteit van leven score waren gerapporteerd voor tenminste 3 maanden follow-up. De data is samengevoegd met behulp van een "random-effects" model en met gewogen gemiddelden. In de analyses werden 3 studies (n=470 patiënten) geïncludeerd in de endovasculaire groep en 5 studies (n=202 patiënten) in de looptrainingsgroep. Vergelijking van de gepubliceerde resultaten van de endovasculaire revascularisatie met die van de looptraining demonstreerde een verbetering in kwaliteit van leven na looptraining, terwijl na endovasculaire behandeling zowel de enkel-arm index (een maat voor functionaliteit) als ook de kwaliteit van leven significant verbeterden. Tussen de behandelgroepen was de enkel-arm index significant hoger na endovasculaire revascularisatie na 3 en 6 maanden, terwijl de gemiddelde verandering in kwaliteit van leven niet significant verschilde na follow-up.

Omdat uit het systematisch literatuur onderzoek bleek dat er weinig consistentie bestaat in de protocollen voor de looptraining die gehanteerd worden in de diverse studies, is er een gerandomiseerde gecontroleerde studie opgezet (**Hoofdstuk 4** en **5**). Deze gerandomiseerde gecontroleerde studie vergeleek de effecten, het klinische succes en de kosten tussen endovasculaire revascularisatie en gesuperviseerde looptraining. Van september 2002 tot september 2005 werden 151 opeenvolgende, nieuwe patiënten met claudicatio intermittens (Rutherford stage 1-3) op de vasculaire polikliniek gerandomiseerd tussen endovasculaire revascularisatie en gesuperviseerde looptraining. De resultaten van deze gerandomiseerde studie lieten zien dat er een klein voordeel was in verbetering van kwaliteit van leven na endovasculaire behandeling na 6 en 12 maanden, maar de verschillen tussen de beide behandelmethoden waren niet statistisch significant. Direct na behandeling was er wel een significant verschil in het klinisch succes in het voordeel van de endovasculaire behandeling, maar na 6- en 12 maanden was dit voordeel verdwenen. De geaccumuleerde winst in kwaliteitsjaren was significant hoger na endovasculaire behandeling dan na gesuperviseerde looptraining na 12 maanden follow-up, maar de kosten na endovasculaire behandeling waren ook significant hoger. Alleen als de maatschappij bereid is om meer dan €77 300 te betalen voor de winst van een kwaliteitsjaar, dan heeft endovasculaire revascularisatie de voorkeur boven gesuperviseerde looptraining als initiële behandelmethode.

Een ander vraagstuk was de invloed van perifeer arterieel vaatlijden op de klinische effectiviteit van een hart revalidatie programma (**hoofdstuk 6**). Bijna de helft van de patiënten die een hart revalidatie start, kan het programma niet succesvol afronden. Patiënten met zowel coronair vaatlijden als perifeer arterieel vaatlijden hebben vaak geen optimaal profijt van de hart revalidatie omdat zij door hun beperkingen hun "target heart rate" niet halen. Het doel van deze studie was evalueren of het klinische effect van een hart revalidatie programma is gerelateerd aan de aanwezigheid van perifeer arterieel vaatlijden. De resultaten van deze studie suggereerden dat het succes van een hart revalidatie programma negatief wordt beïnvloed door de aanwezigheid van perifeer arterieel vaatlijden. Dit betekent dat de patiënten minder voordeel hebben van het programma en een hoger risico lopen op een recidief myocard infarct.

Om de resultaten van hartrevalidatie programma's te verbeteren, hebben we de kosteneffectiviteit van verschillende revalidatie strategieën voor patiënten met zowel coronair vaatlijden als ook perifeer arterieel vaatlijden geëvalueerd. Om de kosteneffectiviteit van verschillende revalidatie strategieën te vergelijken, hebben wij een besliskundig Markov-model ontwikkeld waarmee uitkomsten, zowel kosten als effecten, werden gesimuleerd onder verschillende revalidatie strategieën voor patiënten met perifeer arterieel vaatlijden die een hart revalidatie programma volgden. Het Markov model vergeleek de volgende strategieën: 1. Hart revalidatie (huidige praktijk); 2. Diagnostiek voor perifeer arterieel vaatlijden gevolgd door revascularisatie indien nodig als de patiënt de hart revalidatie vroegtijdig stopt; 3. Diagnostiek voor perifeer arterieel vaatlijden bij alle patiënten voor de aanvang van hart revalidatie en revascularisatie voor perifeer arterieel vaatlijden indien nodig; 4. Een uitgebre-

ide gecombineerde cardiovasculaire revalidatie. De data waren deels afkomstig uit de literatuur en deels uit een database bestaande uit 231 patiënten uit "Advocate Lutheran General Hosptial" (Park Ridge, Verenigde Staten) die een hart revalidatie volgden in 2004. De voor kwaliteit van leven gecorrigeerde levensjaren (QALYs), de "life-time costs" en de incrementele kosten-effectiviteits ratio (ICER) werden vervolgens berekend met behulp van het model. De resultaten van dit model worden gepresenteerd in **hoofdstuk 7**. De resultaten suggereerden dat de behandelstrategieën die de diagnose en zonodig behandeling van perifeer arterieel vaatlijden bevatten, een hogere "net health benefit" opleveren. Dit kan door een gecombineerd cardiovasculaire revalidatie programma, of als dit niet beschikbaar is, door de diagnose en zonodig behandeling van perifeer arterieel vaatlijden als de patiënt het hart revalidatie programma niet succesvol afrondt. Dit zou de kans op een recidief myocard infarct verkleinen en de maatschappij veel kosten kunnen besparen.

In **Hoofdstuk 8** is een diagnostische test evaluatie beschreven. Duplex echografie wordt vaak gebruikt voor de planning van een behandelstrategie voor patiënten met perifeer arterieel vaatlijden. Echter, duplex echografie is onderzoeker afhankelijk en laat geen overzicht zien van het arteriële systeem. We beoordeelden de nauwkeurigheid, voorspellende waarde en variatie tussen de onderzoekers in de beoordeling van de duplex golfvorm als een aanwijzing voor een significante stenose in de aorto-iliacale arteriën. Bij 191 opeenvolgende patiënten (381 aorto-iliacale segmenten) werd de duplex golfvorm van de arteria femoralis communis geclassificeerd als tri-fasisch, bi-fasisch, scherp monofasisch of stomp monofasisch. De golfvormen werden vervolgens vergeleken met de bevindingen van de magnetische resonantie angiografie van het aorto-iliacale segment en de perifere arteriële vaten. We berekenden de diagnostische accuratesse van de golfvorm voor het detecteren van een >50% obstructie van het aorto-iliacale segment en bepaalden de waarnemer variatie tussen de twee waarnemers die de golfvorm hadden beoordeeld en geclassificeerd. De stompe monofasische golfvorm was in 24% aanwezig en bleek een betrouwbare indicatie voor een significante aorto-iliacale obstructie. De scherpe monofasische golfvorm voorspelde betrouwbaar een occlusie van de arteria femoralis superficialis. Echter was dit een kleine subgroep. Er was een goede inter-waarnemer overeenkomst voor het classificeren van de duplex golfvorm. Onze resultaten suggereerden dat de stompe monofasische duplex golfvorm ter plaatste van de arteria femoralis communis een nauwkeurige aanwijzing is voor een aorto-iliacale obstructie, echter de overige golfvormen bleken non-diagnostisch voor het aantonen dan wel uitsluiten van een aorto-iliacale obstructie.

In **Hoofdstuk 9** werden de algemene discussie en de belangrijkste bevindingen van dit proefschrift beschreven. Verder werden relevante methodologische aspecten bediscussieerd tezamen met implicaties voor toekomstig onderzoek en voor de klinische praktijk.

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DANKWOORD

DANKWOORD

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Success consists of going from failure to failure without loss of enthusiasm.

Winston Churchill