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SURVIVAL AND QUALITY OF LIFE AMONG PATIENTS WITH SEVERE LOWER EXTREMITY PERIPHERAL ARTERIAL DISEASE

by

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To Mira, Markus and Linnea

ABSTRACT

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Survival and quality of life among patients with severe lower extremity peripheral arterial disease

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Lower extremity peripheral arterial disease (PAD) is associated with decreased functional status, diminished quality of life (QoL), amputation, myocardial infarction, stroke, and death. Nevertheless, public awareness of PAD as a morbid and mortal disease is low. The aim of this study was to assess the incidence of major lower extremity amputation due to PAD, the extent of reamputations, and survival after major lower extremity amputation (LEA) in a population based PAD patient cohort. Furthermore, the aim was to assess the functional capacity in patients with LEA, and the QoL after lower extremity revascularization and major amputation.

All 210 amputees due to PAD in 1998–2002 and all 519 revascularized patients in 1998–2003 were explored. 59 amputees alive in 2004 were interviewed using a structured questionnaire of QoL. Two of each amputee age-, gender- and domicile-matched controls filled in and returned postal self-administered QoL questionnaire as well as 231 revascularized PAD patients (the amount of these patients who engaged themselves to the study), and one control person for each patient completed postal self-administered QoL questionnaire.

The incidence rate of major LEA was 24.1/100 000 person-years and it was considerably high during the years studied. The one-month mortality rate was 21%, 52% at one-year, and the overall mortality rate was 80%. When comparing the one-year mortality risk of amputees, LEAs were associated with a 7.4-fold annual mortality risk compared with the reference population in Turku. Twenty-two patients (10%) had ipsilateral transversions from BK to AK amputation. Fifty patients (24%) ended up with a contralateral major LEA within two to four amputation operations. Three bilateral amputations were performed at the first major LEA operation. Of the 51 survivors returning home after their first major LEA, 36 (71%) received a prosthesis; (16/36, 44%) and were able to walk both in- and outdoors. Of the 68 patients who were discharged to institutional care, three (4%) had a prosthesis one year after LEA.

Both amputees and revascularized patients had poor physical functioning and significantly more depressive symptoms than their controls. Depressive symptoms were more common in the institutionalized amputees than the home-dwelling amputees. The surviving amputees and their controls had similar life satisfaction. The amputees felt themselves satisfied and contented, whether or not they lived in long-term care or at home. PAD patients who had undergone revascularizations had poorer QoL than their controls.

The revascularized patients' responses on their perceived physical functioning gave an impression that these patients are in a declining life cycle and that revascularizations, even when successful, may not be sufficient to improve the overall function. It is possible that addressing rehabilitation issues earlier in the care may produce a more positive functional outcome. Depressive symptoms should be recognized and thoroughly considered at the same time the patients are recovering from their revascularization operation. Also primary care should develop proper follow-up, and community organizations should have exercise groups for those who are able to return home, since they very often live alone. In rehabilitation programs we should consider not only physical disability assessment but also QoL.

Keywords: Peripheral arterial disease, quality of life, major lower extremity amputation, incidence rate, survival, prosthetic ambulation, revascularization, case-control study.

TIIVISTELMÄ

Leena Remes

Vaikea-asteista alaraajojen valtimokovettumatautia sairastavien potilaiden eloonjääminen, toimintakyky ja elämänlaatu

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Alaraajojen valtimokovettumatautia (ASO) sairastavien potilaiden fyysinen toimintakyky ja elämänlaatu heikentyvät taudin edetessä. Oireettomatkin ASO-tautia sairastavat kuolevat sydän- ja verisuoniperäisiin tauteihin muita useammin. Tämän tutkimuksen tavoitteena oli analysoida ASO-taudin takia tehtyjen reisi- ja sääriamputaatioiden ilmaantuvuus ja uusinta-amputaatioiden määrä. Lisäksi analysoitiin amputaatiopotilaiden eloonjääminen, fyysinen toimintakyky ja elämänlaatu sekä verisuonitoimenpiteissä olleiden ASO-potilaiden elämänlaatu.

Potilasaineiston muodostivat kaikki 210 vuosina 1998–2002 ASO-taudin takia amputoitua ja 519 verisuonitoimenpiteissä vuosina 1998–2003 ollutta turkulaista. Vuonna 2004 elossa olleet 59 amputoitua haastateltiin käyttäen strukturoitua lomaketta. Heidän elämänlaatuaan verrattiin 118 iän ja sukupuolen suhteen kaltaistetun turkulaisen elämänlaatuun. 519:stä verisuonitoimenpiteissä olleesta 231 täytti elämänlaatua käsittelevän kyselylomakkeen, samoin tekivät heidän 231 iän ja sukupuolen suhteen kaltaistettua verrokkiaan. Kyselylomake oli sama kuin amputoituja haastateltaessa käytetty lomake.

Reisi- ja sääriamputaatioiden ilmaantuvuus 24.1/100 000 henkilövuotta (ensimmäinen reisi- tai sääriamputaatio) oli vuosina 1998–2002 suhteellisen suuri. Amputoiduista 21 % kuoli ensimmäisen postoperatiivisen kuukauden aikana ja 52 % ensimmäisen vuoden aikana. Seuranta-ajan kuluessa, (1.1.1998–31.12.2006) 80 % amputoiduista oli kuollut. Amputoitujen ensimmäisen vuoden kuoleman riski oli 7.4-kertainen verrattuna samanikäisiin turkulaisiin. Ipsilateralinen reamputaatio (sääriamputaatiosta reisiamputaatioksi) tehtiin 22 potilaalle (10 %), kontralateralisen alaraajan reamputaatio tehtiin 2-4 amputaatio-operaatiokerralla 50 potilaalle (24 %); kolmelle potilaalle tehtiin primaari bilateraalinen sääri- tai reisiamputaatio. Yhteensä 51 palasi ensimmäisen amputaationsa jälkeen kotiin. Heistä 36 (71 %) sai alaraajaproteesin. Näistä 36:sta 16 (44 %) pystyi kävelemään niin sisällä kuin ulkona. Laitoshoitoon joutuneesta 68 henkilöstä kolmella oli vuoden jälkeen käytössään alaraajaproteesi. Sekä amputoidut että alaraajojen valtimoiden leikkaus- tai pallolaajennustoimenpiteissä olleet kokivat fyysisen kuntonsa huonoksi. Heillä oli yleisemmin depressiivisiä oireita kuin verrokeilla. Laitoshoidossa olevilla amputoiduilla oli yleisemmin masennusoireita kuin kotona asuvilla amputoiduilla. Amputoidut olivat kuitenkin yhtä tyytyväisiä elämäänsä kuin heidän verrokkinsa riippumatta siitä, asuivatko he kotonaan vai laitoksessa. Verisuonitoimenpiteissä olleiden elämänlaatu oli kauttaaltaan huonompi kuin heidän verrokkiensa.

Onnistunutkaan verisuonitoimenpide ei parantanut potilaiden koettua toimintakykyä. On mahdollista, että jos ASO-potilaiden kuntouttavat toimenpiteet aloitettaisiin nykyistä aikaisemmin ja tehokkaammin, nämä henkilöt olisivat nykyistä paremmassa fyysisessä kunnossa. Potilaiden toipuessa verisuonitoimenpiteistä pitäisi myös masennusoireet ottaa huomioon ja pyrkiä hoitamaan niitä samanaikaisesti. ASO-potilaille olisi hyvä järjestää systemaattinen seuranta, esimerkiksi perusterveydenhuoltoon, koska perusterveydenhuolto vastaa kotisairaanhoidosta, ja terveyskeskuksen henkilökunta ja kotisairaanhoidon henkilökunta tekevät jo nytkin koordinoidusti yhteistyötä. Potilaille pitäisi järjestää kuntoryhmiä yhteistyössä kunnan liikuntatoimen kanssa, jolloin potilaat saisivat liikunnan lisäksi vertaistukea. Erityisesti yksinäisyydestä kärsivät hyötyisivät toiminnasta. Kuntoutuksessa tulisi fyysisen kunnon kohentamisen lisäksi ottaa huomioon potilaan itsensä kokema elämänlaatu sekä pyrkiä sen parantumiseen.

Avainsanat: Alaraajojen valtimokovettumatauti, elämänlaatu, reisi- ja sääriamputaatio, ilmaantuvuus, eloonjääminen, alaraajaproteesi, verisuonitoimenpide, tapaus-verrokki tutkimus.

CONTENTS

ABBREVIATIONS

ABI	Ankle-brachial pressure index
ADL	Activities of daily living
AKA	Above knee, transfemoral amputation
ALI	Acute limb ischemia
AMP	Amputee Mobility Predictor
BA	Bilateral amputation
BKA	Below knee, transtibial amputation
BMI	Body mass index
CABG	Coronary artery bypass grafting
CI	Confidence interval
CLI	Critical limb ischemia
COR	Cumulative odds ratio
CVD	Cerebrovascular disease
ECG	Electrocardiogram
GDS	Geriatric Depression Scale
HR	Hazard ratio
LCI	Locomotor Capabilities Index
LEA	Lower extremity amputation
LEGS	Lower Extremity Grading System
LER	Lower extremity revascularization
LS	Life Satisfaction
MMSE	Mini-Mental-State Examination
MOS SF-36	Medical Outcome Study Short Form Health Survey
OR	Odds ratio
PAD	Peripheral arterial disease
PLP	Phantom limb pain
PTA	Percutaneous transluminal angioplasty
QoL	Quality of life
Rand-36 PF	Rand-36 *Physical Functioning* subscale
Rand-36 GH	Rand-36 *General Health* subscale
SMR	Standardized mortality ratio
SSQ6	Six-item Brief Social Support Questionnaire
SSQ6N	Number Score of the six-item Brief Social Support Questionnaire
TBI	Toe brachial index
THL	National Institute for Health and Welfare
TUG	Timed "Up-and-Go" Test

WIQ	Walking Impairment Questionnaire
VO2max	The maximal rate at which oxygen can be taken up, distributed and used by the body during physical activity. VO2max is expressed in terms of milliliters of oxygen consumed per kilogram of body weight per minute.
15D HRQoL	Fifteen dimension health-related quality of life
6 MW	Six-Minute Walk Test

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original articles, referred to in the text by their Roman numerals I to IV. In addition, some unpublished data are presented.

I **Leena Remes**, Raimo Isoaho, Tero Vahlberg, Heikki Hiekkanen, Kimmo Korhonen, Matti Viitanen, Päivi Rautava. Major lower extremity amputation in elderly patients with peripheral arterial disease: incidence and survival rates. Aging Clinical and Experimental Research 2008;20(5):385–393.

II **Leena Remes**, Raimo Isoaho, Tero Vahlberg, Matti Viitanen, Päivi Rautava. Predictors for institutionalization and prosthetic ambulation after major lower extremity amputation during an eight-year follow-up. Aging Clinical and Experimental Research 2009;21(2):129–135.

III **Leena Remes**, Raimo Isoaho, Tero Vahlberg, Matti Viitanen, Markku Koskenvuo, Päivi Rautava. Quality of life three years after major lower extremity amputation due to peripheral arterial disease. Aging Clinical and Experimental Research. Accepted for publication 2009. http://www.ncbi.nlm.nih.gov/pubmed/20009496?dopt=Citation

IV **Leena Remes**, Raimo Isoaho, Tero Vahlberg, Matti Viitanen, Päivi Rautava. Quality of life among lower extremity peripheral arterial disease patients who have undergone endovascular or surgical revascularization: a case-control study. European Journal of Vascular and Endovascular Surgery. Accepted for publication 2010. http://dx.doi.org/10.1016/j.ejvs.2010.03.028

1. INTRODUCTION

Peripheral arterial disease (PAD) is a manifestation of systemic atherosclerosis that is common and associated with an increased risk of death and ischemic events (Diehm et al., 2004a). The underdiagnosis of PAD among practicing physicians may be a barrier to the effective prevention of ischemic cardiovascular events associated with PAD (Hirsch et al., 2001; Hirsch et al., 2007). Diagnosing and identifying PAD could be improved by using a simple ankle-brachial pressure index (ABI) measurement (Kennedy et al., 2005; McDermott et al., 2004). Atherosclerosis risk factors are very prevalent in PAD patients, but these patients receive less intensive treatment for lipid disorders and hypertension and are prescribed antiplatelet therapy less frequently than patients with cerebrovascular and cardiovascular disease (Norgren et al., 2007).

PAD comprises obstruction of blood flow in arteries other than the coronary and intracranial vessels. Although the definition of PAD technically includes problems within the extracranial carotid, upper limb, visceral, and renal arteries, it is the circulation of the lower limbs that is most frequently involved (Ouriel, 2001). Atherosclerosis most often causes chronic PAD (Diehm et al., 2004a; Dormandy and Murray, 1991). Patients with PAD can be classified into groups according to symptom severity. One half of patients older than 55 years are asymptomatic (Diehm et al., 2004a). Of the symptomatic patients, approximately 40% experience intermittent claudication, and 10% have critical limb ischemia (CLI). Intermittent claudication results from poor oxygenation of the muscles of the lower extremities and is experienced typically as an aching pain, cramping, or numbness in the calf, buttock, hip, thigh, or arch of the foot. Symptoms are induced by walking or exercise, and are relieved by rest (Norgren et al., 2007). CLI is again the term used to designate the condition in which PAD has resulted in resting leg or foot pain, or in a breakdown of the skin of the leg or foot, causing ulcers or tissue loss (Lumsden et al., 2009).

Risk factors for PAD are similar to those for atherosclerosis in coronary and cerebrovascular beds. The two most important risk factors for PAD are cigarette smoking and diabetes (Hiatt et al., 1995). In addition, hypertension, dyslipidemia, elevated C-reactive protein, hyperviscosity and hypercoagulable states, hyperhomocysteinemia, and chronic renal insufficiency have been identified as risk factors (Kennedy et al., 2005). Until now there has been a constant lack of preventive strategies in decreasing vascular risk factors among patients with symptomatic PAD who are at an increased risk of recurrent vascular events (Aronow, 2005; Hirsch et al., 1997).

Asymptomatic PAD is a significant predictor of cardiovascular morbidity and mortality. In high-risk subjects, measurement of the ABI provides valuable information on future cardiovascular events. (Hooi et al., 2004) The ABI should become routine screening among patients with diabetes/and/or those who smoke (Eason et al., 2005).

In order to improve the QoL of patients with a severe or still less severe state of PAD, primary prevention of the disease should be the main target. Detecting asymptomatic arteriopathy, i.e. stage I of the Fontaine classification early enough, and treating PAD in time as well as PAD awareness amongst both health care professionals and the general population is required. PAD awareness is e.g. more monitoring of the ankle-brachial pressure index, particularly among diabetics, smokers, and the over 70s than is presently being done in order to detect PAD patients. ABI-measurements should be organized at health centers in the same way as ECGs.

The survival of persons with symptomatic PAD is poor (Dormandy et al., 1999b; Hirsch et al., 2001). The annual cardiovascular mortality rate derived from epidemiological studies of patients with stable symptomatic PAD is 4–6% and is higher in those with a more severe disease (Criqui et al., 1992). For patients with CLI, the annual cardiovascular mortality rate is 25%, and may be as high as 45% in those who have undergone amputation (Criqui et al., 1992; Luther, 1994).

The outcome for patients undergoing intervention for CLI is determined by the measures of reconstruction patency and limb salvage. However, chronically ill patients with several comorbidities have easily defined functional, ambulatory impairments, which predict the survival (Taylor et al., 2006). The Six-Minute Walk Test provides prognostic information regarding mortality in persons with PAD also beyond that provided by the ABI (McDermott et al., 2008). Such functional health-related quality of life (HRQoL) measures as the Walking Impairment Questionnaire (WIQ) or the Rand-36 *Physical Functioning* subscale have discriminative ability to find the functional disabilities typical of PAD patients (Regensteiner et al., 2008).

Assessment of psychosocial status together with functional capacity in PAD patients is important. Depression is common in PAD (Smolderen et al., 2008; Thomas et al., 2004). Hence, depressive symptoms, may also be interpreted to explain the poor adherence to the recommended behavior and lifestyle changes (Kronish et al., 2006), which may in turn contribute to adverse physical outcomes in depressed patients with PAD (Smolderen et al., 2008). Cognitive impairment (Rafnsson et al., 2009) cannot be overlooked. It may e.g. hinder a prosthesis donning, and naturally community living, especially if the person lives alone. Assessing the important spectrum of quality of life (QoL), including the perceived social support, then becomes valuable.

2. REVIEW OF THE LITERATURE

This review discusses the comprehensive way of assessing the QoL of patients with severe PAD. Existing recommendations for treating PAD are available for all, e.g. renewed TransAtlantic Inter-Society Consensus (TASC) (Dormandy and Rutherford, 2000; Norgren et al., 2007; Rutherford et al., 1997). The review describes a decision-making process based on the algorithm (Figure 1), which ends on a revascularization treatment. This thesis goes beyond the algorithm, to the prognosis after a lower extremity revascularization (LER) or amputation (LEA). The rehabilitation process after these interventions should proceed under the proper guidance of primary health care professionals and community according to the limits and visions planned multidisciplinarily, to assure the patient achieves the best possible quality of life, no matter how short his or her life would be.

2.1. Epidemiology of lower extremity peripheral arterial disease

2.1.1 Peripheral arterial disease prevalence

PAD prevalence is 2.5% at ages 40 to 59 years, 8.3% at ages 60 to 69 years, and 18.8% at ages 70 to 79 years. Prevalence is higher in men than in women. (Criqui et al., 1997). In the German Epidemiological Trial on Ankle Brachial Index Study (2002) a total of prevalence of PAD for men/women as indicated by AB1<0.9 was 19.8/16.8%, respectively. Patients with PAD were slightly older than patients without PAD and suffered more frequently from diabetes, hypertension, lipid disorders, and other coexisting atherothrombotic diseases, (any cerebrovascular event; any cardiovascular event) (Diehm et al., 2004b). Examples of PAD prevalence studies are presented in Table 1**.**

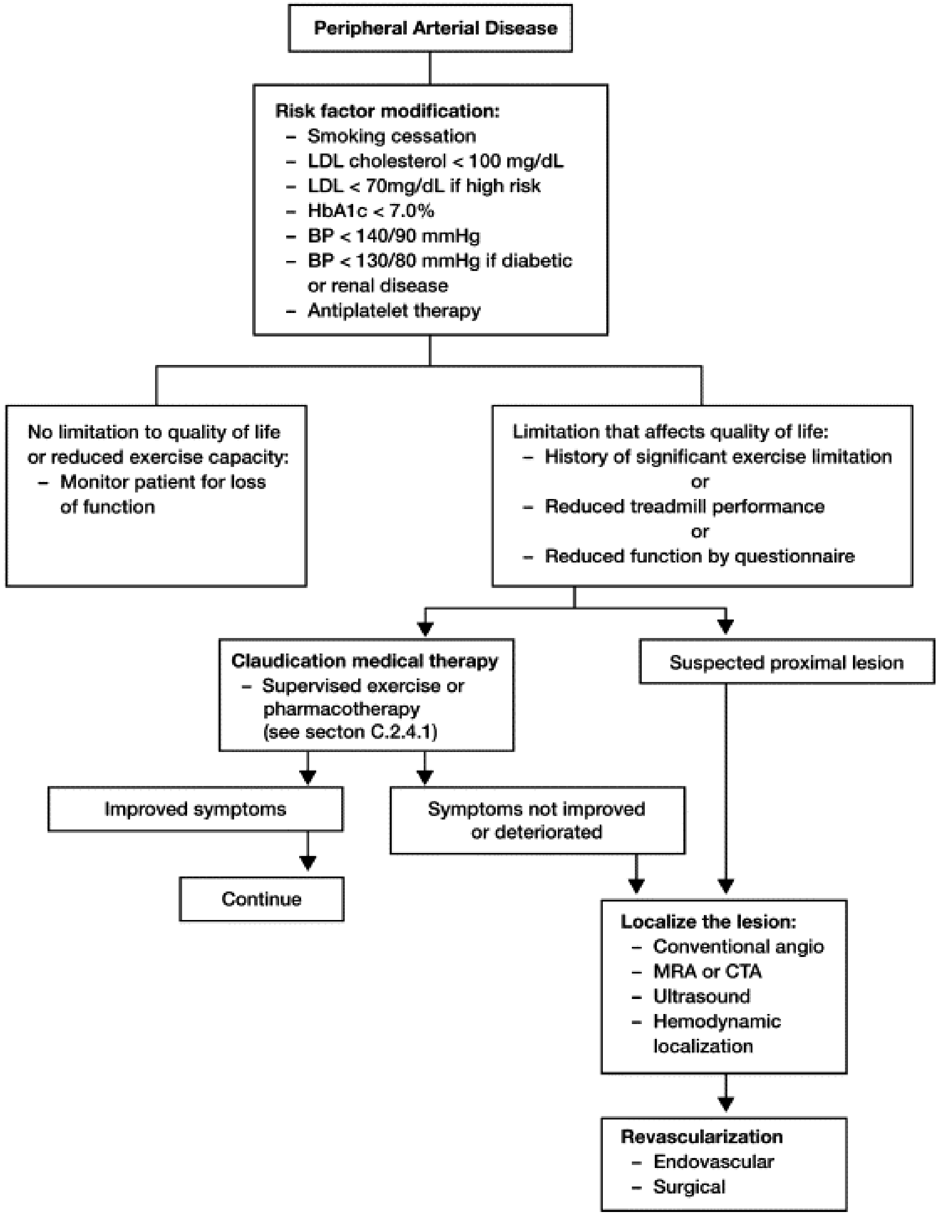

Figure 1. C3. Overall treatment strategy for peripheral arterial disease. BP=blood pressure; HbA1c=hemoglobin A1c; LDL=low density lipoprotein; MRA=magnetic resonance angiography; CTA=computed topographic angiography. (Hiatt, 2001) Reproduced with the permission of the copyright holder.

Table 1 Leg symptoms and lower extremity peripheral arterial disease in defined study populations.

Study	Population screened	Criteria of PAD	Prevalence of PAD	Prevalence of leg symptom categories among individuals with PAD
Community-dwelling men and women				
Cardiovascular Health Study (Newman et al., 1993)	5888 men and women who are age 65 or older and randomly sampled from the community	ABI[1]≤0.9	12.4%	Atypical exertional leg pain 32.3%, asymptomatic 59.1%, intermittent claudication 8.6%
Women's Health and Aging Study (McDermott et al., 1999)	1002 disabled women age 65 and older living in and around Baltimore.	ABI[1]<0.9	35%	Any exertional leg pain 33%, asymptomatic 67%
Men and women identified from primary care practice				
PARTNERS (Hirsch et al., 2001)	6979 men and women in primary care practices across the USA. Participants were either (a) aged 50-69 with a history of diabetes mellitus or smoking history of 10 pack years[2] or (b) age 70 and older.	ABI[1]<0.9	29%	Newly diagnosed PAD: Atypical exertional leg pain 46.3%, asymptomatic 48.3%, intermittent claudication 5.5%, previously diagnosed PAD: Atypical exertional leg pain 61.7%, asymptomatic 25.8%, intermittent claudication 12.6%
German Epidemiological Trial on Ankle Brachial Index (getABI study) (Diehm et al., 2004b)	6880 patients were included (42.0% men, mean age 72.5 years, mean body mass index 27.3 kg/m^2, mean systolic/diastolic blood pressure 143.7/81.3 mmHg).	ABI[1]<0.9	men/women as 19.8/16.8%	
Men and women identified from noninvasive vascular laboratories				
San Diego population (Criqui et al., 1996)	368 men and women with PAD identified from a noninvasive revascularization: vascular laboratory		100% by definition	Prior LER: Exertional leg pain other than intermittent claudication 37.9%, asymptomatic 29.4%, intermittent claudication 33.7% No prior LER: Exertional leg pain other than intermittent claudication 47.3%, asymptomatic 32.1%, intermittent claudication 23.6%
Walking and Leg Circulation Study (WALCS) (McDermott et al., 2001a)	Men and women age 65 and older identified from noninvasive vascular laboratories at three Chicago-area hospitals		100% by definition	Leg pain on exertion and rest 19.1%, atypical exertional leg pain/carry-on 8.9%, atypical exertional leg pain/stop 19.6%, asymptomatic 20%, intermittent claudication 32.6%

[1]Ankle-brachial pressure index

[2]A pack year is a quantification of cigarette smoking. A way to measure the amount a person has smoked over a long period of time. It is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. For example, 1 pack year is equal to smoking 20 cigarettes per day for 1 year, or 40 cigarettes per day for half a year, and so on.

The prevalence of PAD increases with age, thus it is expected to increase in community as the population gets older (Diehm et al., 2004a).

2.1.2 Classification by the severity of peripheral arterial disease

A suggested classification for grading the severity of chronic PAD for the purposes of standardized reporting practices is outlined below. The original Fontaine classification (Table 2) was based on clinical information only (Fontaine et al., 1954).

Table 2 Fontaine classification of lower extremity peripheral disease

Stage	Symptoms	Signs
Stage I	Asymptomatic arteriopathy	
Stage II	Exercise-induced ischemia	
IIa	Intermittent claudication, pain during walking Relief of symptoms when standing Compensated disease: walking distance >100 m	
IIb	Decompensated disease: walking distance <100m	
Stage III	Ischemia-driven symptoms at rest	
IIIa		Ankle Pressure Index ≥ 50 mm Hg
IIIb		Ankle Pressure Index < 50 mm Hg
Stage IV	Loss of sensation to the lower part of the extremity	Trophic ulcers and gangrene
IVa		Limited gangrene
IVb		Extensive gangrene

The classification proposed by Rutherford and his co-workers (Table 3) distinguishes between minor tissue loss and major tissue loss as well as between mild, moderate and severe claudication. It comprises six clinical categories, and its use is recommended by the Trans-Atlantic Inter-Society Consensus (TASC) Working Group for the diagnosis and assessment of the progression of PAD. (Rutherford et al., 1997)

Table 3 Clinical categories of chronic limb ischemia

Grade	Category	Clinical description	Objective criteria
0	0	Asymptomatic-no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise[1]; AP after exercise >50 mm Hg, but at least 20 mmHg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise[1] *and* AP after exercise <50 mm Hg
II[2]	4	Ischemic rest pain	Resting AP <40 mm Hg, flat or barely pulsatile ankle or metatarsal PVR; TP <30 mm Hg
III[2]	5	Minor tissue loss —non-healing ulcer, focal gangrene with diffuse pedal ischemia	Resting AP <60 mm Hg, ankle or metatarsal PVR flat or barely pulsatile; TP <40 mm Hg
	6	Major tissue loss —extending above TM level, functional foot no longer salvageable	Same as category 5

AP=Ankle pressure, PVR=pulse volume recording, TP=toe pressure, TM=transmetatarsal
[1]Five minutes at 2 mph on a 12 % incline
[2]Grades II and III, categories 4, 5, and 6 are embraced by the term (chronic) critical ischemia

In Rutherford's classification, symptomatic disease is stratified into six categories to provide the greater breadth required for many clinical research reports. Thus, categorical clinical improvement is made possible within the broad healing of claudication by subdividing it into three levels and gangrene is divided into two levels according to its extent and the possibility of salvaging a functional foot remnant. Simpler broader gradations, based on Fontaine's original clinical staging, are offered in parallel. In both, a zero category or grade has been used to identify those who have no symptoms, or merely sensations of coldness and either no clinical signs of occlusive disease or modest pulse diminution. Such a category or grade is valuable because it also allows postoperative improvement to be gauged at all levels. However, this results in different numbers being assigned to the Fontaine-equivalent grades than has become common practice in Europe. Although it has become common practice in Europe to divide patients with claudication (grade I) into two levels (Fontaine stages IIa and IIb) to indicate disability, such an imprecise separation is not recommended. (Rutherford et al., 1997)

2.1.3 Critical limb ischemia

Critical limb ischemia (CLI), i.e. Fontaine stages III and IV and Rutherford, category 4 and category 5 and 6, is associated with great loss of both limb and life. The majority of CLI patients (58-85%) have tissue loss or gangrene in their leg (Biancari et al., 2000). Reports on incidence of CLI have ranged from 500 to 1000 per million inhabitants per year, and the prevalence has been estimated to be 1 per 2500 inhabitants (Dormandy and Rutherford, 2000). In Finland, about 2600-5300 people have each year CLI (Albäck, 2009). Thirty per cent of the CLI patients have DM (Criqui et al., 1997).

2.1.4 Acute limb ischemia

Acute limb ischemia (ALI) denotes a quickly developing or sudden decrease in limb perfusion, usually producing new or worsening symptoms and signs, and often threatening limb viability (Norgren et al., 2007). ALI is caused by abrupt occlusion of a major artery. ALI may also occur as the result of an embolic event or a local thrombosis in a previously asymptomatic patient (Table 4) (Dormandy et al., 1999a; O'Connell and Quinones-Baldrich, 2009). There is little information on the incidence of ALI, but a few national registries and regional surveys suggest that the incidence is around 140/million/year. ALI due to emboli has decreased over the years, possibly as a consequence of less cardiac valvular disease from rheumatic fever and also better monitoring and anticoagulant management of atrial fibrillation. Meanwhile, the incidence of thrombotic acute leg ischemia has increased. The clinical manifestations of ALI are listed in Table 5. ALI often occurs at the end of life. In such cases, lower limb ischemia results from a gradual slowdown in the functioning of the organs. (Bergqvist, 2007)

Table 4 Common causes of acute limb ischemia

Embolism	Thrombosis
Atherosclerotic heart disease	Atherosclerosis
Coronary artery disease	Low-flow states
Acute myocardial infarction	Congestive heart failure
Arrhythmia	Hypovolemia
Valvular heart disease	Hypotension
Rheumatic	Hypercoagulable states
Degenerative	Vascular grafts
Bacterial	Progression of disease
Congenital	Intimal hyperplasia
Prosthetic	Mechanical
Artery-to-artery	Arterial plaque rupture
Aneurysm	Trauma
Atherosclerotic plaque	Aortic/arterial dissection
Idiopathic	External compression
Iatrogenic	Iatrogenic
Paradoxical embolus	
Trauma	
Other	
Air, amniotic fluid, fat, tumor, chemicals, drugs	

Table 5 Clinical manifestations of acute arterial embolism versus thrombosis

Embolism	**Thrombosis**
Arrhythmia	No arrhythmia
Sudden onset	Sudden or slower onset
Severe signs and symptoms	Less severe signs and symptoms
No history of claudication, rest pain	History of claudication, rest pain
No risk factors for PAD[1]	Risk factors for PAD
Normal contralateral pulse exam	Abnormal contralateral pulse exam
No physical findings of CLI	Physical findings of CLI[2]

[1]Cardiac disease, prior myocardial infarction, hyperlipidemia, stroke, family history, history of smoking, diabetes, etc.
[2]Absence of extremity pulses, diminished hair growth, thin skin, thick nails, and ulcers.
(O'Connell and Quinones-Baldrich, 2009)

2.2. Diagnosing peripheral arterial disease

A thorough physical exam is necessary to begin to look for signs of PAD and to grade its severity. Furthermore, if there is any suspicion of PAD, ABI measurements should be made easily available at the country's main health centers. A comprehensive assessment of PAD patients should also include a patient's subjective opinion on his or her health status whereby the use of appropriate scales is worth considering.

2.2.1 Ankle-brachial pressure index

In diagnosing PAD, ABI is an effective non-invasive screening tool (Diehm et al., 2004a). It should be used to systematically detect patients with so far unrecognized PAD from all those who smoke or have diabetes mellitus and are 50 years or older, from diabetics with over 20 years of duration of disease, from all patients 70 years or older, and from any patient with exertional leg pain (Norgren et al., 2007) (Figure 2). Screening ABI from only those who have symptoms naturally misses asymptomatic PAD; in other words those patients who, however, are in an increased risk of cardiovascular events (Diehm et al., 2009) and busy palpation of the distal pulses is not accurate enough when 12-15% of the distal pulses are falsely not detected (Dormandy, 1992).

An ABI greater than 0.90 is considered normal; greater than 0.70 to 0.89 is considered mild disease; 0.5 to 0.69, moderate disease; and less than 0.5, severe disease (Dormandy and Rutherford, 2000).

Compared with angiography, the sensitivity of a low ABI for leg artery stenosis of ≥ 50% is about 90%, and the specificity is about 98% (Yao et al., 1969). It is difficult to predict the risk of deterioration in a recent claudicant (Dormandy et al., 1999c). A changing ABI is possibly the best individual predictor, because if a patient's ABI rapidly deteriorates it is most likely to continue to do so in the absence of successful treatment (Rutherford et al., 1997). It has been shown that in patients with intermittent claudication, the best predictor of deterioration of PAD (and hence e.g. need for LER or major LEA), is an ABI of <0.50 with a hazard ratio of more than 2 compared to patients with an ABI >0.50. Studies have also indicated that in those patients with intermittent claudication in the lowest strata of ankle pressure (i.e. 40-60 mmHg), the risk of progression to severe ischemia or actual limb loss is 8.5% per year. (Norgren et al., 2007) Therefore, Doppler ultrasound measurement for ABI determinations is a non-invasive, inexpensive, reliable tool in primary care and enables general practitioners to identify patients at risk of PAD (Diehm et al., 2008; Holland-Letz et al., 2007; Norman et al., 2004).

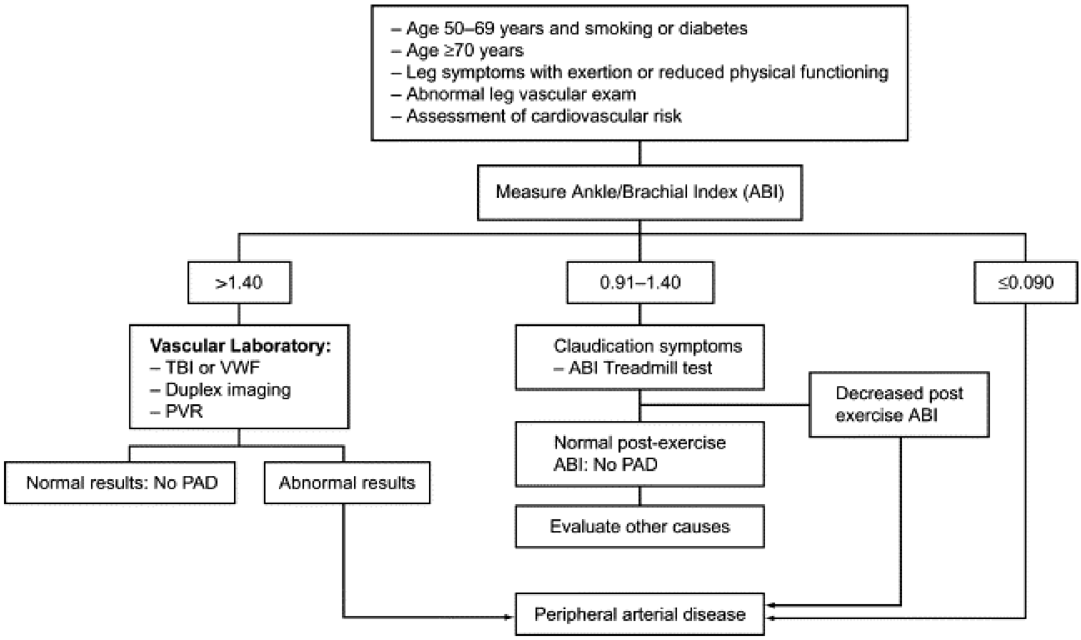

Figure 2. Algorithm for diagnosis of lower extremity peripheral arterial disease (PAD). ABI=ankle-brachial pressure index; TBI=toe brachial index; VWF=velocity wave form; PVR=pulse volume recording. (Hiatt, 2001) Reproduced with the permission of the copyright holder.

ABI can be falsely elevated (>1.40) due to medial arterial calcification, which complicates clinical decision-making and PAD diagnosis. In such cases, since medial arterial calcification does not usually affect toe vessels, the measurement of toe pressures and toe brachial index (TBI) is recommended. (Mayfield et al., 1998) The association between elevated ABI (already ≥1.3) and poor survival is similar to that of low ABI. PAD appears to be an independent risk factor for mortality among patients with elevated ABI (Suominen et al., 2010).

2.2.2 Comprehensive assessment of peripheral arterial disease patients

A comprehensive PAD patient assessment is a *sine qua non* for the post intervention rehabilitation. This assessment could contain such measures that are essential to assess recuperative possibilities of a patient.

2.2.2.1 Measuring cognitive ability

The Mini-Mental-State Examination (MMSE) (Folstein et al., 1975) is a very important scale for screening cognitive impairment of the elderly people. Sum scores of 24-30 are considered indicative of no cognitive impairment and 18-23 of mild and 0-17 of severe cognitive impairment (Tombaugh and McIntyre, 1992). Patient-based studies have shown that individuals with severe PAD tend to perform poorly on cognitive tests compared to controls (Tilvis et al., 2004). In population studies, PAD is associated with an increased cognitive decline independently of previous cerebrovascular disease and cardiovascular risk factors. A low ABI may be an early predictor of cognitive decline and of potential value in identifying individuals at increased risk of cognitive impairment. In patients with PAD, secondary preventive measures directed at decreasing the long-term systemic vascular complications may also be important to the preservation of cognitive health (Rafnsson et al., 2009).

2.2.2.2 Measuring physical functional status

If the assessment is performed multidisciplinarily, it should include all important measures to evaluate a possible PAD in the elderly patient. Most of the measures may also be found from the internet, e.g. as the Geriatric Examination Tool Kit (http://web.missouri.edu/~proste/tool/). The two tests below have been also used in validating the Locomotor Capabilities Index (LCI) and the Amputee Mobility Predictor (AMP). They are functional tests excellent for evaluating PAD (McDermott et al., 2008; Montgomery and Gardner, 1998).

Timed "Up-and-Go" Test

In the Timed "Up-and-Go" (TUG) Test the participant is asked to, as fast as possible, rise from a chair, walk three meters with his/her ordinary walking aid, turn around, walk back and sit down again in the chair and the result is measured in seconds. The TUG Test is easy to use in clinical settings and it has been shown to be valid and reliable in testing of function in an elderly population. (Podsiadlo and Richardson, 1991) The TUG Test is a reliable instrument with adequate concurrent validity to measure the physical mobility of patients with an amputation of the lower extremity (Schoppen et al., 1999).

Six-Minute Walk Test

The Six-Minute Walk Test (6 MW) gives a good impression of the remaining exercise capacity of an elderly patient with chronic heart failure, while a treadmill exercise test with VO2max measurement is difficult to accomplish. The 6 MW is on the other hand well correlated with the treadmill test. The 6 MW is also well tolerated by elderly patients (Peeters and Mets, 1996). The 6 MW yields highly reliable measurements, which are related to the functional and hemodynamic severity of PAD, in patients with intermittent claudication (Montgomery and Gardner, 1998). Walking performance in PAD patients who complete 6 minutes of walking is largely determined by a decline in walking velocity rather than slower initial walking velocity. ABI is more closely associated with cadence than step length (McDermott et al., 2001b). By studying 6 MW, in 2004, McDermott and her co-workers have found that the baseline ABI and the nature of leg symptoms predict the degree of functional decline, so that the lack of worsening in claudication symptoms over time in patients with PAD may be more related to declining functional performance than to the lack of disease progression (McDermott et al., 2004). In 2008, McDermott et al. have demonstrated that the supervised 6 MW among persons with PAD also predicts mortality independently of the ABI (McDermott et al., 2008).

Treadmill testing

Serial treadmill testing is an objective means of assessing changes in performance in patients with claudication. The two measures most commonly used to evaluate exercise performance on the treadmill are claudication-free walking time or distance and maximal, claudication-limited walking time or distance (absolute claudication distance). The latter measure is used most frequently in clinical trials as the primary end point. (Nehler et al., 2003b)

Evaluating prosthesis use capability

Several indices have been created in order to evaluate patients' physical capability to use a prosthesis. These include, e.g.:

Locomotor Capabilities Index

The Locomotor Capabilities Index (LCI) consists of 14 items that measure one general construct, the locomotor capabilities with the prosthesis. Two subscales emerge from this general construct; basic abilities (7 items) and advanced abilities (7 items). The items inquire about the ability to perform activities and the level of independence while performing these activities. Each of the 14 items is graded on a 4-point ordinal scale; 0 (not able to), 1 (yes, with help from other person), 2 (yes, with supervision) and 3 (yes, independently). The total LCI score is the sum of the item scores and can range from 0 (worst) to 42 (best). Similarly, subscale scores for basic and advanced capabilities with the prosthesis can range from 0 to 21. The LCI is intended for self-administration but can also be administered in a face-to-face or telephone interview. The time needed to complete the LCI is approximately five minutes (Grise et al., 1993; Gauthier-Gagnon and Grise, 1994).

The Locomotor Capabilities Index is routinely used, e.g., in Orton, Helsinki, Finland (Määttänen, 2006).

Amputee Mobility Predictor

The Amputee Mobility Predictor (AMP) instrument is designed to measure ambulatory potential of lower-limb amputees with and without the use of a prosthesis. The AMP instrument is easy to administer in 15 minutes or less, with a simple scoring system, requiring very little equipment or space. It has a high inter- and intrarater reliability and appears to be a very practical clinical tool. Its high reliability suggests that, with proper training, multiple disciplines could administer the test with results that are consistent over time. (Gailey et al., 2002)

Prosthesis usage classification

In this classification, class I means ambulating with prosthesis and without any other walking aids outdoors and indoors, class II means ambulating with prosthesis indoors, but requiring one walking stick or crutch for outdoor activities, class III means independent indoors, ambulating with prosthesis and one crutch indoors, but requiring two crutches outdoors and occasionally a wheelchair, class IV means walking indoors with a prosthesis and two crutches or a walker, but requiring a wheelchair for outdoor activities, class V means walking indoors only short distances, but mostly a wheelchair user. Class VI means walking with aids, but without prosthesis, and a class VII patient ambulates with a wheelchair only. (Narang et al., 1984; Pohjolainen et al., 1990)

2.2.2.3 Measuring quality of life

QoL and health-related QoL (HRQoL) instruments abound in health care literature, but many appear to measure nothing more than what in previous decades was called health status (Dijkers, 2003). HRQoL assessments aim to provide a multidimensional measure of patient health with regards to illness and response to treatment, and include physical, emotional, and social domains (Criqui et al., 1992; Regensteiner and Steiner, 1990). Patient self-reported health-status questionnaires, whether filled out by patients or administered in by person or by phone, fall into two categories: (*a*) generic questionnaires designed to scale any burden of disease or disability and (*b*) disease specific questionnaires designed to measure health states related to a given medical condition. Generic questionnaires allow comparisons across many patient populations, whereas disease specific questionnaires are more sensitive to particular changes in the health burden of a particular condition. (Gallagher and Desmond, 2007)

Usually, PAD patients have multiple morbidities, and the assessment of QoL may give a more representative picture of the patient's perception of health than the exclusive measurement of walking performance. However, a number of unresolved questions prevent the use of QoL as a primary end point after intervention. Problem areas include choosing the most appropriate instrument, proper validation of scales, potential compositing of end points, and the definition of what magnitude of change with a specific QoL scale may be considered clinically relevant. At present, QoL should be assessed as a secondary end point (O'Neill, 1997).

Examples of generic quality of life instruments

Generic measures of QoL typically assess multiple health domains and can be used in the general population and across different patient populations (Garratt et al., 2002)

Medical Outcome Study Short Form 36 or Rand-36

The most widely used, validated, and reliable generic questionnaire is the Medical Outcome Study Short Form Health Survey (MOS SF-36) described and analyzed by Ware and Sherbourne (Ware and Sherbourne, 1992). The Rand-36 is identical to the MOS SF-36 (Aalto, 1999). This 36-item questionnaire, which refers to patients' health over the previous four weeks, was originally designed to measure general health perceptions and eight particular dimensions of health: physical functioning, mental health, role-emotional functioning, role physical functioning, bodily pain, vitality/fatigue, and social functioning. The *Physical Functioning* subscale (PF) is based on a standardized, 10-item scale that asks respondents to rate their degree of difficulty in performing vigorous and moderate activities, lifting or carrying, climbing stairs, bending, kneeling or stooping, walking three distances (ranging from one block to one mile), and bathing or dressing. The 10 responses are scored from 0 (very limited in all 10 items) to 100 (not limited at all for all 10 items). It also correlates well (r=0.68) with 6 MW results in medically managed claudication patients (Bauman and Arthur, 1997).

15D health-related quality of life instrument

The 15D HRQoL instrument is widely used in Finland. It is a Finnish scale which reliability, validity, discriminatory power and responsiveness to change of its health state descriptive system and valuation system is described by Sintonen (Sintonen, 2001). The 15D is a non-disease specific, 15-dimensional, standardized and self-administered measure of HRQoL that can be used both as a profile and single index score measure.

HRQoL among elective coronary artery bypass grafting (CABG) patients has been evaluated by using the 15D instrument. CABG patients experience a significant improvement in their HRQoL within 6 months after the operation, and the effect remained through the observation period between 6 to 18 months, but in patients 75 years or over, the initial improvement of HRQoL returned to the preoperative level 18 months after the surgery. (Loponen et al., 2007).

Furthermore, the psychometric properties of the 15D HRQoL instrument are analyzed, and 15D is also found to be appropriate for measuring among patients with PAD. By using the 15D instrument and the Nottingham Health Profile (NHP) instrument, Koivunen et al found that the HRQoL of middle-aged men with PAD was significantly poorer than that of their controls, and that male sex, retirement, asymptomatic walking distance, other atherosclerotic disease, lack of exercise, and feeling incapable of performing daily activities were also important causes of impaired HRQoL. (Koivunen and Lukkarinen, 2006)

Trinity Amputation and Prosthesis Experience Scales

The Trinity Amputation and Prosthesis Experience Scales (TAPES) is a multidimensional assessment of adaptation to amputation and prosthesis use developed specifically for use with individuals with lower limb amputations. The TAPES comprises three *Psychosocial Adjustment* subscales, three *Activity Restriction* subscales and three *Prosthesis Satisfaction* subscales. The final section of the TAPES includes an assessment of other medical problems and phantom and residual limb pain experience. Details of the psychometric characteristics and validity and reliability data can be found on the internet (The TAPES is freely available and can be downloaded at www.tcd.ie/psychoprosthetics). (Gallagher and Maclachlan, 2004)

An example of instruments for the perceived functional status

There are a number of subjective, patient self-reported methods being used to evaluate functional endpoints. These measures address functional endpoints that are crucial for patients who cope with difficulties such as crossing a busy street before a traffic light changes or putting on pants while standing. (Feinglass et al., 2000b)

Walking Impairment Questionnaire

Because PAD is associated with limited physical capacity and impaired functional status (Holtzman et al., 1999), the Walking Impairment Questionnaire (WIQ) is optimal in evaluating walking limitations in patients with PAD (Regensteiner and Steiner, 1990). It assesses the ability of individuals to walk defined distances (ranging from inside the home to five blocks, walking slowly to running or jogging) and speeds, and a 3-item scale of difficulty in climbing one to three flights of stairs.

In addition, the questionnaire evaluates symptoms (e.g. calf pain, shortness of breath, chest pain, joint pain) that could limit ambulation. The WIQ has been validated against treadmill walking as well as the 6 MW, 4-meter walking velocity test, and ABI. It is used to evaluate baseline functional status and efficacy of treatments for claudication.

Patients with particular comorbid conditions may provide characteristic responses to WIQ items (Feinglass et al., 1999). The WIQ therefore also assesses whether claudication, as opposed to other comorbidities, is indeed the most limiting symptom for patients' walking ability. The WIQ walking distance and speed scores and PAD patients' distance on supervised 6 MW and 4-meter walking velocity tests have reasonably high correlations (McDermott et al., 1998).

Examples of instruments for the perceived mental status

There are several depression screening tools, e.g., Center for Epidemiologic Study Depression Scale (Darnall et al., 2005), Beck Depression Inventory (Beck et al., 1961), and Zung Self-Rating Depression Scale (Zung, 1967). The screening tools and PAD's association with depression is found in more detail in Pratt and her co-workers' article (Pratt et al., 2005).

A screening of depression as e.g. by using Geriatric Depression Scale (GDS) (Yesavage et al., 1982) is essential in order to treat and support the PAD patient most properly. The relationship between depression and vascular disease should be understood as bidirectional (Vaccarino et al., 2001). Depression predisposes to later vascular disease and vascular disease may lead to or aggravate depressive symptoms (Thomas et al., 2004). A checklist assessing the amount of depressive symptoms may be more useful than a dichotomous diagnosis. From a practical standpoint, the GDS test is easier to administer than a structured interview for clinical diagnosis of depression, and it does not require a mental health specialist. Therefore, it may provide a feasible means of identifying depressed patients with PAD who are in need of special attention. (Thomas et al., 2004) Among men and women with PAD, the prevalence of a clinically significant number of depressive symptoms measures by GDS is high, 12% - 24%. Greater numbers of depressive symptoms are associated with greater impairment in lower extremity functioning. (McDermott et al., 2003) PAD patients with depression are also at a significantly increased risk for coronary heart disease events and progression of contralateral PAD after their LER (Cherr et al., 2008).

Self-reported Life Satisfaction Score

A summary score for life satisfaction (LS) is defined as interest in life, happiness, loneliness, and general ease of living (scale range 4-20). The summary score may be divided in three categories: the satisfied (LS 4-6), the intermediate group (LS 7-11), and the dissatisfied (LS 12-20). (Koivumaa-Honkanen, 1998)

The role of self-reported life satisfaction in mortality with a prospective cohort study (1976-1995) has been investigated. A nationwide sample of healthy adults (18-64 years, n=22 461) from the Finnish Twin Cohort responded to a questionnaire about life satisfaction and known predictors of mortality in 1975. Dissatisfaction was found to associate with increased disease mortality, particularly in men with heavy alcohol use (hazard ratio=3.76, 95% CI: 1.61, 8.80). Women were not found to show similar associations between life satisfaction and mortality. Life dissatisfaction may predict mortality and serve as a general health risk indicator. The effect seems to be partially mediated through adverse health behavior. (Koivumaa-Honkanen et al., 2000)

Examples of instruments for the perceived social support

A variety of measures have been used to assess the effects of social support on physical and psychological well-being (Unden and Orth-Gomer, 1989). They include the Multidimensional Scale of Perceived Social Support (MSPSS) (Asano et al., 2008; Zimet et al., 1990) and Sarason's social support questionnaire with 27 items or the short form of 6 items (SSQ6), which have number and satisfaction parts (Sarason, 1987).

The 6-item Brief Social Support Questionnaire (SSQ6) is an example of many perceived social support scales. Sarason's Social Support Questionnaire has high internal validity (Sarason, 1987). The use of only the number part of the score has been utilized in previous studies in Finland. They represent large populations (Elovainio et al., 2003; Väänänen et al., 2008; Väänänen et al., 2005; Vahtera et al., 2002). The predictive value of the lack of social support, measured by using the SSQ6, has been shown on psychiatric morbidity (Morano et al., 1993; Pierce et al., 1992).

2.2.3 Examples of grading systems to predict the adverse events or survival after lower extremity revascularization

When decision-making is to be done with a severe PAD, some grading systems relying on long experience and scientific evidence are worthwhile.

1) A risk score has been collected from the Finnvasc registry. Diabetes, coronary artery disease, foot gangrene, and urgent operation, which are the most important predictors of 30-day postoperative mortality and/or a major LEA after infrainguinal surgical revascularization for CLI, comprise the score. The risk score has been developed by assigning one point to each of the

predictors. The score is validated, and the method is found to be useful in stratifying immediate postoperative outcome after infrainguinal surgical revascularization. (Biancari et al., 2007)

2) Prevent III (PIII) CLI is a risk score in infrainguinal bypass for amputation free survival after LER. There four points is given for dialysis, three points for tissue loss, and one point for both age ≥75 years and advanced coronary artery disease. A patient has got a low risk with ≤ 3 points, a medium risk at 4-7 points, high risk at ≥8 points for LEA (Schanzer et al., 2009; Schanzer et al., 2008)

3) The Lower Extremity Grading System (LEGS) Score (Kalbaugh et al., 2004) consists of 1) angiographic finding, 2) clinical presentation, 3) preoperative functional status (ambulatory, home-bound or transfer only), 4) comorbid conditions, and 5) various technical factors (Figure 3). It has been used successfully as a treatment standardization tool for PAD whether to suggest open surgery versus endovascular intervention versus primary amputation, in patients with medically refractory, lifestyle limiting intermittent claudication, or limb-threatening ischemia.

The LEGS (Lower Extremity Grading System) Score:

Arteriographic Findings		Presentation		Functional Status		Co-morbidities*		Technical Factors	
- Aortic		- Claudication	5	- Ambulatory	0	- Obesity	2	All Cases	
<3 cm aortic stenosis/ occlusion or 3-5 cm stenosis of aorto-iliac bifurcation	8	- Limb threatening ischemia	2	- Ambulatory/ at home only	2	- High risk coronary artery disease	3	- Redo Surgery	2
								- Redo angioplasty	-2
>3 cm aortic stenosis/ occlusion or > 5 cm stenosis of aorto-iliac bifurcation	0			- Non-ambulatory/ transfer only	5	- Age > 70	1	Infrainguinal Cases - Blind segment target	2
- Iliac				- Non-ambulatory	20	> 80	2	- No venous conduit	6
TASC A or B	8							- No vein w/ foot Infection	8
TASC C	2								
TASC D	0								
or									
- Fem-pop-tib									
<5cm occlusion/stenosis	5								
>5cm occlusion w/ distal target	0								
Isolated common/deep femoral stenosis	0								
>5cm occlusion w/o distal target	6								
Possible score:	0-8	Possible score:	2-5	Possible score:	0-20	Possible score:	0-7	Possible score:	-2-12

Recommended Treatment: (sum of total score from each column)
- 0 – 9 = open surgery
- 10 – 19 = endovascular
- ≥20 = primary amputation

* If a heel ulcer and ESRD are present, double the score

Figure 3. Lower Extremity Grading System. *TASC*, Trans-Atlantic Intersociety Consensus; *Fem-pop-tib*, femoral-popliteal tibial; *Redo*, repeat. (Kalbaugh et al., 2004) Reproduced with the permission of the copyright holder.

It might also be possible for a general practitioner or even a rehabilitation specialist to estimate the patient's situation in three out of the five columns of the LEGS score, i.e. presentation, functional status and comorbidities; and to leave arteriographic findings and technical factors to the vascular clinics (Figure 3). The three column message could be gathered in the referral letter for the vascular surgeon.

2.3. Treating peripheral arterial disease patients

Comprehensive treatment of risk factors for cardiovascular disease in patients with atherosclerosis is fundamental. Smoking cessation is the most important measure for treating all types of vascular disease and cannot be overemphasized. Regular physical exercise and walking alleviates the symptoms of an existing PAD. Weight loss and physical activity also improve risk factors such as hypertension, high lipids, and high blood sugar.

All lifestyle changes should be regarded as a long-term investment, not as temporary restrictions or attitudes.

2.3.1 Risk factor management/modification and treating comorbidites

Modifiable risk factors that predispose individuals to PAD include active cigarette smoking, passive smoking, diabetes mellitus, hypertension, dyslipidemia, increased plasma homocysteine levels and hypothyroidism. Comorbidities such as hypertension, diabetes mellitus, dyslipidemia, and hypothyroidism require treatment. Statins reduce the incidence of intermittent claudication and improve exercise duration until the onset of intermittent claudication in people with PAD and hypercholesterolemia. Anti-platelet drugs such aspirin or especially clopidogrel, angiotensin-converting enzyme inhibitors and statins should be given to all patients with PAD. Beta blockers are recommended if a coronary artery disease is present. (Aronow, 2009) Patients with PAD do not achieve risk factor control as frequently as individuals with coronary heart disease or cerebrovascular disease. Improved risk factor control associates with a positive impact on 1-year cardiovascular event rates (Cacoub et al., 2009).

In all Fontaine classification's stages, all PAD risk factors should be carefully recorded and evaluated during appointments. When we treat PAD patients, we do not only care about their medication, but also ask the patients about their smoking habits. If they do smoke, guidance to help them quit smoking should also be given. Ascertaining whether patients move daily, and instructing them to join exercise groups organized in the community is also vital.

The medical management of patients with severe PAD is essential, even when their disease has led to an amputation. E.g. statins and antiplatelet agents are also then needed. (Bradley and Kirker, 2006)

2.3.2 Exercise therapy

Treatment options for intermittent claudication include bypass surgery, angioplasty and drug therapy, but the mainstay of treatment for many patients with mild-to-moderate claudication remains as advice "Stop smoking and keep walking" (Housley, 1988). Exercise therapy is a relatively inexpensive, low risk treatment, compared with interventional procedures (Oakley et al., 2008). Regular supervised exercise can improve walking distance (Gardner and Poehlman, 1995), and it should be made available as part of the initial treatment for all patients with PAD. The most effective programs employ treadmill or track walking that is of sufficient intensity to bring on claudication followed by rest over the course of a 30-60 minute session. Exercise sessions are typically conducted three times a week for 3 months. (Norgren et al., 2007) Exercise therapy should play an important part in the care of selected patients with intermittent claudication to improve walking times and distances. Effects are demonstrated following three months of supervised exercise although some programmes have lasted over one year. There are limited data to suggest that an effect is sustained for up to two years. (Watson et al., 2008)

Proper exercise rehabilitation should be used for Fontaine class IIa and IIb and possibly rest pain/ class IIIa patients also together with social interventions and personal support.

2.3.3 Invasive treatments

Invasive treatments are presented here as LERs and LEAs. The increasing safety of vascular interventions should be considered when deciding which patients to treat, but with the caveat that endovascular interventions are not always safer than open repair (Nowygrod et al., 2006).

2.3.3.1 Lower extremity revascularization

LER is indicated to prevent limb loss in patients with CLI caused by arterial occlusive disease, including patients with chronic distal leg wounds (a non-healing amputation site or ulcers that fail to heal over time), wet or dry gangrene of the toes and forefoot, or ischemic rest pain (Feinglass et al., 2000b). Revascularization to improve blood flow can be either open or endovascular. Open revascularization is surgical reconstruction of the artery by means of bypass, endarterectomy or thromboembolectomy. Bypass involves rerouting the stenosis or occlusion using a vein or synthetic vascular prosthesis, whereas endarterectomy involves surgical removal of stenotic or occlusive atherosclerotic lesion from inside the artery. Thromboembolectomy is the removal of clots from the artery either surgically (with Fogarty's catheters) or endovascularily (by aspiration catheters).

Patients with thrombotic or macroembolic events should also be considered candidates for urgent reconstructive surgery. Arterial reconstructive surgery is often undertaken in selected patients with severe, disabling intermittent claudication. Patients with non-healing wounds, gangrene, or ischemic rest pain are likely to harbor occlusive disease at multiple levels. These patients may require staged arterial reconstruction. Patients with extensive tissue loss invariably require pulsatile blood flow to heal their wounds. Catheter-based interventional procedures, such as percutaneous transluminal angioplasty (PTA) of the aortoiliac segment, femoropopliteal segment as well as infrapopliteal arteries with or without stenting; have become established alternatives to surgical revascularization in recent years. (Feinglass et al., 2000b)

SBU Board of Directions and Scientific Advisory Committee, Sweden, / The Swedish Council on Technology Assessment in Health Care has made a systematic review 'Peripheral Arterial Disease– Diagnosis and Treatment', in 2007 (Bergqvist, 2007). In the summary the grade of evidence of revascularization interventions has been set as follows:

Key conclusions about invasive treatment for symptomatic PAD:

- Open LER improves walking distance better than walking training in claudication patients for whom invasive treatment is indicated (Evidence Grade 3). Scientific evidence is insufficient to assess whether open LER reduces the risk of amputation in patients with CLI.
- The scientific evidence is insufficient to assess the efficacy of endovascular LER in patients with intermittent claudication and CLI.
- Active treatment of ALI leads to amputation free survival after one year in 65–80% of cases. There is no decisive difference between open and endovascular LER (thrombolysis therapy) in terms of amputation-free survival (Evidence Grade 2).
- The amputation incidence after active treatment in patients with ALI is 3–12% after 30 days and 10–30% after one year. Following treatment for ALI, 4–11% of patients die within 30 days and 6–42% within one year (Evidence Grade 2).
- Patients with milder forms of ischemia – either in terms of duration (1–2 weeks) or clinical degree (without blisters or muscle soreness) – have a higher incidence of amputation free survival (Evidence Grade 3).
- No decisive differences in treatment results have been found between thrombosis, embolism and graft occlusion – three separate causes of ALI (Evidence Grade 3).
- The scientific evidence is insufficient to assess whether various techniques of catheter-delivered endovascular therapy (thrombolysis) yield similar results.
- Catheter-delivered endovascular therapy (thrombolysis, locally and arterially) gives rise to a higher incidence of local bleeding than open revascularization in acute occlusion (Evidence Grade 3).
- The scientific evidence is insufficient to determine whether increased vascular surgery can reduce the number of amputations in the general population.
- A platelet inhibitor increases the percentage of open bypass reconstructions below the groin (Evidence Grade 3).
- Therapy with a vitamin K antagonist does not appear to be more effective than platelet inhibitors with respect to open reconstruction (Evidence Grade 3).
- Bleeding complications more frequently accompany therapy with a vitamin K antagonist than with a platelet inhibitor (Evidence Grade 2).
- Open or endovascular LER improves QoL in patinets who have PAD, with intermittent claudication and CLI (Evidence Grade 3).

(Bergqvist, 2007)

2.3.3.2 Major lower extremity amputation

According to the internet medical dictionary major lower extremity amputation is defined as "amputation, removal of an appending part (appendage), above the ankle joint". Many reports, however, also consider amputation at the ankle joint to be considered as a major amputation. This level is mainly used in amputation due to trauma or congenital deformities (Pohjolainen, 1993).

Despite developments in balloon angioplasty and peripheral vascular bypass grafting, PAD accounts for 90% of the causes of the amputations in the elderly population (Fletcher et al., 2002). With the changes in population demographics, the number of individuals older than 65 continues to increase and the absolute number of geriatric patients with amputation might remain large (Feinglass et al., 1999; Fletcher et al., 2002). Individuals with diabetes have a 15- to 46-fold risk of all LEAs than those without (Armstrong et al., 1997). As to ABI recordings, patients with an ABI < 0.5 are more likely to require amputation (Marston et al., 2006).

Unfortunately, patients who present with CLI and physiologic impairments that preclude open surgery commonly also seem to have such comorbidities that blunt any functional advantage achieved after percutaneous transluminal angioplasty (PTA) for limb salvage. A PTA in that kind of a setting affords very little benefit compared with amputation alone. (Taylor et al., 2007b) Major tissue loss, end-state renal disease, diabetes mellitus, and non-ambulatory status are all such factors where treatment with primary amputation might be the choice rather than revascularization (Abou-Zamzam et al., 2007).

The goal of modern management of patients who have had an amputation is to restore the form and function of the limb in a way that optimizes QoL (Matsen et al., 2000). Therefore, amputation surgery should be the first step in the rehabilitation of a patient with a non-functional limb, rather than the final step in treatment (Pinzur et al., 2003). When faced with a difficult decision regarding LEA compared with attempted limb reconstruction, expectations for a reasonable outcome must be determined. After reasonable goals have been set, the surgery should be directed toward interfacing with a prosthetic limb. Current surgical techniques of LEA, paying special attention to transosseous versus disarticulation amputation, help to optimize prosthetic limb fitting and functional rehabilitation. (Pinzur et al., 2003)

Incidence of major lower extremity amputation

In 2005, there were 1.6 million persons in the USA living with the loss of a limb. Of those subjects, 38% had an amputation secondary to PAD with a comorbid diagnosis of diabetes mellitus, (i.e. 608 000 persons). It is projected that the number of people living with the loss of a limb will more than double by the year 2050 to 3.6 million. If incidence rates secondary to PAD can be reduced by 10%, this number would be lowered by 225 000 (i.e. 3 375 000 US citizens with limb loss in 2050.) (Ziegler-Graham et al., 2008)

The reported incidence of LEA varies considerably between different Western countries, both between and within countries (Table 6). Variations in the clinical decisions made by vascular surgeons given to the same patient are likely to explain at least a part of the observed geographical variation in LEA rates. (Connelly et al., 2001)

Table 6 Some amputation rates reported during the past decade

Report	Year	District/country	Amputation rate	Case definition
(Luther et al., 2000)	1993-1994	Finland	216/1000 000 inhabitants/year	Major amputations due to PAD
(Siitonen et al., 1993)	1978-1992	Eastern Finland catchment area	26.9/100 000 inhabitants/year	Toe and leg amputations due to PAD separating diabetics and non-diabetics
(Lääperi et al., 1993)	1989	Southern Finland catchment area	amputation rate 22.0/100 000	All amputations and all etiologies
(Pohjolainen and Alaranta, 1999)	1995	Southern Finland catchment area	28.0/100 000 inhabitants	All amputations and all etiologies
(Eskelinen et al., 2001)	1997-2000	Seinäjoki Central Hospital and Ähtäri District Hospital	annual incidence 29.5 to 15.2/100 000 inhabitants/year	All amputations and all etiologies
(Eskelinen et al., 2004)	2000	Southern Finland catchment area	15.4/100 000 inhabitants/year	All amputations and all etiologies
(Ebskov et al., 1994)	1983 1990	Denmark	34.5/100 000 25.0/100 000	Amputations due to PAD
(Pernot et al., 2000)	1994	Holland	17.1 per 100 000	Amputation levels: 77 transtibial, 52 transfemoral and 43 knee disarticulation; major amputations only.

Amputation and revascularization activity

Among patients aged over 75 years there has been a decrease in both revascularization procedures and amputation rates to levels in 2007 –the lowest for 14 years (McCaslin et al., 2007). The rates of major amputations have significantly fallen for women under 70 years of age and for men under 80 years during 13 years of follow-up starting in 1983 (Mattes et al., 1997). At the same time, there has been a significant fall in non-amputation vascular surgery for individuals under the age of 60. In addition, rather than an overall rise in surgery there has been shift away from sympathectomy and thrombendarterectomy to angioplasty and bypass surgery. Furthermore, an increasing proportion of all major amputations have had a prior attempt at arterial reconstruction. According to Mattes and his co-workers' observations the decrease in major amputations for PAD may reflect a fall in the incidence of PAD, possibly by being aided by more effective surgery, rather than increased rates of vascular surgery (Mattes et al., 1997). On the other hand, the national volume of major amputations per US capita (100 000 population, age >40 years) has decreased by 38%, and the volume for the US national and regional use of endovascular LER is doubled (Egorova et al., 2010). Ergonova and her co-workers have also found that 1) the volume of open LER had decreased by 67% from 1998 through 2007; 2) ambulatory endovascular LER, i.e. for intermittent claudication increased by nearly 50%; 3) interventions have declined by 20% (93% to 75%) for CLI. On the other hand, outpatient data analysis has revealed a fivefold increase in vascular interventions for CLI and intermittent claudication, in the US, endovascular LER interventions have quadrupled (8% to 32%) for CLI and doubled (26% to 61%) for intermittent claudication. A parallel reduction has occurred in major amputations for patients with CLI (42% to 30%), for other PAD diagnoses (18% to 14%), and for intermittent claudication (0.9% to 0.3%). Surgical interventions for CLI have declined significantly for octogenarians from 317 to 240 per 100 000, but outpatient interventions have increased for CLI, intermittent claudication, and other diagnoses in all age groups. Comorbidities for patients treated have substantially increased, but for most procedures, cardiac and bleeding complications have significantly decreased during the last decade. It includes changes in medical management and wound care. In-hospital length of stay has declined there from 9.5 to 7.6 days and the percentage of short (1-2 day) hospitalizations has increased from 16% to 35%. The authors confess that the change appears to be largely due to the widespread and successful use of endovascular LER or to earlier intervention, or both, driven by the safety of these techniques. (Egorova et al., 2010)

Reamputations

Several studies have reported reamputation rates (Dillingham et al., 2005; Thomas et al., 2001). However, the results of these studies are too general to apply to individual patients; some studies combine reamputation episodes of both ipsilateral and contralateral limbs (Larsson et al., 1998) and others addressed reamputation of only one extremity (Bodily and Burgess, 1983). Izumi and his co-workers in the USA, in 2006 have defined a reamputation episode as the removal of bones to advance on amputation a level higher. Any soft tissue surgeries such as debridement, incision and drainage, or secondary closure are excluded, as well as revision surgeries performed at the same level. The last level of amputation is not counted as a reamputation if the amputation was performed on the same limb within a 2-week period. All minor and major amputations are included into their study protocol. They report on reamputation episodes for the ipsilateral and contralateral limbs performed on 277 diabetic patients after their first LEA between 1993 and 1997. The cumulative rates of reamputation per person were 26.7% at 1 year, 48.3% at 3 years, and 60.7% at 5 years, and hence of ipsilateral major LEA reamputation: 4.7, 11.8, and 13.3%, respectively, and for contralateral major LEA reamputation: 11.6, 44.1, and 53.3%. Their study showed that a patient is at the greatest risk for further same-limb amputation in the six months after the initial amputation. Their opinion was that although the risk to the contralateral limb rises steadily, it never meets the level of that of the ipsilateral limb. Therefore, the focus should be on preventive efforts and medical resources during individualized at-risk periods for patients undergoing first-time amputations. (Izumi et al., 2006)

In 1980, in Denmark, the incidence of ipsilateral reamputation was high in the immediate postoperative period with 10.4% after one month, 16.5% after three months and 18.8% after six months. Later ─after the amputation─ the incidence decreased and reached a total of 23.1% after four years. The risk of contralateral amputation was then 11.9% within one year, 17.8% after two years, 27.2% after three years, and finally 44.3% after four years. (Ebskov and Josephsen, 1980)

In some cases the selection of the original amputation level may leave patients with non-healing stumps, thereby necessitating reamputation. For an amputation to be successful patients must comply with wound care and off-loading, and careful discharge planning and patient education may be necessary for a better outcome in this period. (Izumi et al., 2006)

2.4. Mortality

PAD is associated with increased mortality. The severity of PAD by e.g. Fontaine classification and the comorbidities affect the mortality.

2.4.1 Mortality in critical limb ischemia

CLI is a serious condition if left untreated. If there is no chance for revascularization, the survival of the patient is poor, and the 1-year survival plus limb salvage is only 28% (Mätzke et al., 1996). Nevertheless, mortality is expected to be 20% within the first year of presentation, and 40–75% are likely to die within five years (Luther et al., 2000). Diabetes, smoking, and one or more cardiovascular risk factor [angina, myocardial infarction, arrhythmia and congestive heart disease (Eagle and Froehlich, 1996)] are all predictors of mortality in CLI. Patients with CLI have an elevated risk of future myocardial infarction, stroke, and vascular death, 3-fold higher than patients with intermittent claudication. (Novo et al., 2004)

2.4.2 Mortality in acute limb ischemia

Patients presenting with ALI continue to have a particularly severe short-term outlook both in terms of loss of the leg and mortality, with 30-day amputation rates of between 10% and 30% and a mortality rate of around 15%. A patient with an embolic cause for an ischemic leg is at a higher risk of death because of the associated underlying cardiac disease, whereas patients with a thrombotic cause are more likely to lose a limb. The fact that overall mortality rates after intervention for acute ischemia have not improved dramatically over the past 20 years no doubt reflects the severity of the underlying diseases in these high-risk patients (Dormandy et al., 1999a; O'Connell and Quinones-Baldrich, 2009)

2.4.3 Mortality and its predictors after lower extremity revascularization

Survival after LERs is poor, only a 60–70% five-year survival is reported in most surgical series (Duggan et al., 1994; Farkouh et al., 1994). This fact particularly complicates clinical decision-making for the oldest patients, who have the worst long-term prognosis but may require LERs to achieve a level of walking ability and exercise capacity consistent with maintaining general cardiovascular health (Taylor et al., 2005b).

At primary presentation, severe comorbidities, tissue loss, or the presence of gangrene, as well severe coronary heart disease (Schanzer et al., 2009), are bound to lead to poor outcome (Taylor et al., 2007a). Perioperative cardiac factors (age, preoperative risk level, early cardiac complications) are the primary determinants of patient longevity (Back et al., 2004). Thus, cardiovascular risk factor management in patients with CLI is important before revascularization (Bismuth et al., 2001; Schouten et al., 2010).

Diabetes plus poor perioperative glycaemic control associates with an unfavorable outcome after infrainguinal bypass surgery in diabetic patients (Malmstedt et al., 2006). Diabetes is associated with lower amputation-free survival after leg bypass for CLI. That is why patients with diabetes and limb ischemia need intensified treatment of diabetes-related risk factors to improve outcome (Malmstedt et al., 2008).

Renal insufficiency is a risk factor for poor outcome after infrainguinal bypass in patients with CLI (Arvela et al., 2008; Taylor et al., 2007a). Also patients with extracardiac arteriopathy, diabetes and decreased glomerular filtration rate at the time of coronary artery bypass grafting (CABG) are at risk for late lower limb ischemia. These patients would most benefit from closer follow-up for prevention of PAD and its related complications. (Biancari et al., 2008)

However, when taking into account the ambulatory ability at the time of presentation only impaired ambulatory ability associates with death in 70% of the patients in 5 years, and presence of dementia with late mortality in 73% (Taylor et al., 2006).

2.4.4 Mortality and its predictors after lower extremity amputation

The mean survival of LEA patients ranges between two and five years (Pernot et al., 1997; Kulkarni et al., 2006; Ploeg et al., 2005). Advanced age predicts mortality after major LEA (Ebskov, 1999; Lavery et al., 1996; Mayfield et al., 2001; Stone et al., 2006). There is a high risk of mortality in the first year for renal disease, cardiovascular disease, and proximal amputation level, while there is no increased risk for persons with diabetes during the first year following amputation, but the risk increases thereafter (Lavery et al., 1997; Lavery et al., 1996; Mayfield et al., 2001; Stone et al., 2006; Subramaniam et al., 2005). The fact that a person's condition does not allow him or her to return home after LEA, quantifies that the patient's ability is decreased to the level dependency of being institutionalized, which is found to predict mortality (Lavery et al., 1996).

In a ten year follow-up on the survival after LEA due to all causes, there were altogether 705 patients from Southern Finland with LEAs in 1984–1985 (Pohjolainen and Alaranta, 1998). Vascular reconstructions, arterial embolectomy, thrombendarterectomy, lumbar sympathectomy or a combination of these had preceded the amputation in 168 cases (24%) of all the patients. Seventy-three patients had undergone a LEA before 1984. Thirty-two of them were due to PAD, and in 40 cases due to diabetes without a PAD diagnosis. Of the 304 PAD patients, 43% died within the first postoperative year, 43% lived over two years, and 23% lived longer than five years. Of the diabetics handled separately from the PAD patients 38% died within the first postoperative year, 47% lived longer than two years, and 20% longer than five years. The median survival for PAD patients was 1 year 6 months and for diabetics 1 year 11 months. (Pohjolainen and Alaranta, 1998)

The mortality rate during the first postoperative year is high (Table 7).

Table 7 Mortality after LEA reports from the Nordic countries

Report	Year	District/country	1-year survival	2-year survival	Case definition
(Lääperi et al., 1993)	1989	Southern Finland	64%	53%	79% of the amputations were performed due to for PAD
(Pohjolainen and Alaranta, 1999).	1995	Southern Finland	60%		All amputated people
(Eskelinen et al., 2004)	2000	Southern Finland	48%		PAD LEA patients
(Ebskov, 1999)	1982-1992	Denmark	SMR[1] 8.6 during the 1st year	SMR 3.2 during the 2nd year	

[1]Standard mortality rate

2.5. Functional outcome and its predictors after invasive treatments in severe peripheral arterial disease

Functional outcome for patients undergoing LER for CLI is not solely determined by the traditional measures of reconstruction patency and limb salvage, but also by certain intrinsic patient comorbidities at the time of presentation (Taylor et al., 2006). Preoperative functional status (especially ambulatory status at presentation; ambulatory, home-bound, 'transfer-only'/ non-ambulatory) is the most important predicting factor of the functional outcome after LER or LEA (Taylor et al., 2005b). If the ambulatory ability is poor at the time of presentation, the patient coming for the intervention impaired ambulatory ability leads in 39.5% failure to eventually ambulate (hazard ratio, HR 2.83). In the presence of dementia 41.2% eventually fail to ambulate (HR 2.20) (Taylor et al., 2006) Taylor and his co-workers have reported on outcomes after 1000 treated limbs with rest pain (35.5% with endovascular, 61.7% with open surgical revascularization, and 2.8% with both): At 5 years, the survival was only 41,9% and limb salvage 72.1%; 70.6% of those alive had maintained ambulation, and 81.3% their independent living status (Taylor et al., 2006).

Holtzman and his co-workers (1999) have assessed functional status and QoL outcomes after LER by a telephone survey and chart review in Minnesota, USA. There were 329 subjects who had undergone either their first LER procedure or a primary LEA for PAD between 1998 and 1995 and who had granted consent or had died. 166 patients (50%) were alive and were surveyed by telephone in 1996 (the follow-up examination was done 1 to 7.5 years after the qualifying procedure).

Seventy-three per cent of the 166 patients (121/166) still had the qualifying limb, 65% of them (108/166) were able to walk independently and 43% (71/166) had little or no limitation in walking several blocks. Patients with diabetes and patients who were older were less likely to be able to walk at follow-up examination and had a worse functional status. The number of years since the procedure was not a predictor in any of the analyses. Holtzman and his co-workers conclude that the survivors are likely to retain their limb over time and have good functional status; and that number of years since the procedure is not a predictor of the functional outcome. (Holtzman et al., 1999)

Even the most updated literature involves a small number of patients and does not operate with uniformly defined outcomes rendering a direct comparison among studies difficult and causing low external validity. Also the assessment of functional outcome of patients after LEA has been carried out differently. That is why studies are not always comparable with each other. (Cao and De Rango, 2009; Pernot et al., 1997)

2.5.1 Discharge after lower extremity revascularization or major amputation

The functional outcome after LER or LEA may be adversely estimated by patients' capability to return home or being forced to move into an institution, thus losing their independent living status. After LER there is a 30% possibility with a hazard ratio of 7.97, of losing independent living status if the ambulation is preoperatively impaired. But the presence of dementia increases the risk of losing independent living status by 46%, with a hazard ratio of 5.44 (Taylor et al., 2006). In 1998, Pomposelli and his co-workers reported on results of patients 80 years or older in the USA who had undergone LER. Residential status and level of ambulatory function were graded by a simple scoring system in which 1 indicates living independently, walking without assistance; 2 indicates living at home with family, walking with an ambulatory assistance device; 3 indicates an extended stay in a rehabilitation facility, using a wheelchair; and 4 indicates permanent nursing home, bedridden. Preoperative and postoperative scores for both residential status and ambulatory function were compared. The patient survival rate at 5 years was 44%. The postoperative residential status and ambulatory function scores were 1.95+/-0.80 and 1.70+/-0.66, respectively. The overall scores remained the same or improved in 88% and 78% of patients, respectively. The authors mean that LER in octogenarians is safe, with graft patency, and limb salvage is comparable to those reported for younger patients. LER preserves the ability to ambulate and reside at home for most patients (Pomposelli et al., 1998).

Discharge to a nursing home after major LEA again is common with females, advanced age (>65 years), single marital status, high level amputation, and advanced cerebrovascular disease and locomotor impairment, while male gender, and absence of advanced locomotor impairment are associated with discharge to a rehabilitation facility (Lavery et al., 1997).

According to Taylor and his co-workers predicting factors for a failure to maintain independent living status after LEA are in the order of importance 1) age ≥70 yrs, 2) age 60-69, 3) the level of amputation, 4) being ‘homebound, but ambulatory status’, and 5) presence of dementia (Taylor et al., 2005a).

2.5.2 Prosthesis usage predictors

The functional outcome after LEA is most often described as a capability to be able to ambulate with a prosthesis. However, for those who are non-ambulatory already before LEA and also homebound, the ambulatory status predicts not wearing a prosthesis. E.g., in Helsinki a rehabilitation model was formed to improve prosthetic use in 2005. Of the 79 amputees, only 40% were ambulatory, i.e. possible prosthetic use candidates. (Määttänen, 2006) Serious comorbidities, such as severe coronary heart disease and end-state-renal disease predict the non-wearing (Taylor et al., 2005a). All cerebrovascular diseases associate with the inability to be fitted with a prosthesis (Steinberg et al., 1985). Instead, a working capacity of 50% VO2max or greater, a lesser number of comorbidity, good ability to stand on the remaining leg, and a strong will to walk are positive predictors for prosthesis use (Chin et al., 2002). Whilst a larger amount of physical disability, cognitive impairment/ presence of dementia, poorer self-perceived health and the amputee's dissatisfaction predict the non-wearing of a prosthesis (Bilodeau et al., 2000; Schoppen et al., 2003; Taylor et al., 2005a).

The level of amputation predicts the mobility after LEA; BK gaining better mobility than AK (Taylor et al., 2005a; Turney et al., 2001). Following contralateral amputation barely more than half are able to walk. (Inderbitzi et al., 1992; Taylor et al., 2005a). As far as the stump is concerned, no residual contracture of the knee or hip joint are predicting factors for successful prosthetic ambulation (Munin et al., 2001). Even though there are different opinions about the mobility outcome following BK or AK amputations, it has also been found there are no significant perceived rehabilitation benefits in preserving stump length; i.e. by performing a BK amputation may not be as significant as previously reported (Basu et al., 2008). One-leg balance on the unaffected limb is an excellent predictor of the future prosthesis use (Schoppen et al., 2003). Failing to ambulate correlates with poor wound healing, and in that case not necessarily with etiology or surgical level (Munin et al., 2001). Also possession of a wheelchair is found to predict the non-wearing of a prosthesis (Bilodeau et al., 2000). However, when amputation is inevitable, more consideration should be given to surgery that optimizes wheelchair rehabilitation (Houghton et al., 1992).

In 1991, in a 1-year follow-up after LEA, Pohjolainen and Alaranta found that on 125 survivors increasing age associates with decreased physical function: i.e. walking distance, walking time, amount of walking outdoors, and use of a prosthesis. The need for walking aids increases with older people. The time lag between surgery and prosthetic fitting, and the occurrence of cerebrovascular disease associate with lesser prosthetic usage. In the group of BK amputees the length of the stump had a significant favorable relationship with walking distance. Male smokers with BKAs had a shorter walking distance and they were not able walk outdoors as much as the BK amputated non-smokers. None of the variables showed any significant relationship with the postoperative accommodation situation. (Pohjolainen and Alaranta, 1991)

A physiologic limit to successful prosthetic fitting may exist in the geriatric patient due to advanced age and comorbidity (Frieden, 2005). Research should be directed toward improving outcomes of postamputation rehabilitation in elderly patients and in devising alternatives to long-term care as the number of these patients increases (Fletcher et al., 2002). It is important to take the patient's comorbidity factors and expected mobility outcome into consideration when deciding on the primary amputation level (Basu et al., 2008).

2.6. Quality of life outcome after invasive treatments in severe peripheral arterial disease

Long-term follow up studies seem to be scares on QoL after LER or LEA.

2.6.1 Expressed on a generic scale

In a prospective study, Koivunen and Lukkarinen followed 64 conservatively, 85 endovascularily and 31 surgically treated patients for one year with a generic QoL measure, the Nottingham Health Profile (NHP) questionnaire and an ABI measurement before treatment and 12 months after. The ABI and asymptomatic walking distance scores of the patients treated with endovascular and surgical procedures improved statistically significantly. Conservatively treated patients reported improvement of sleep and emotional reactions. The patients with endovascular treatment reported improved emotional reactions, energy and less social isolation. The surgically treated patients reported improvement of pain, mobility, sleep and emotional reactions. Deterioration of any clinical characteristics or HRQoL was not observed after any of the treatment modalities. They conclude that surgery gives PAD patients a good clinical outcome and HRQoL for at least a year, whereas patients who were treated with endovascular and especially conservative treatment gained limited benefits. (Koivunen and Lukkarinen, 2008)

2.6.2 Expressed as patient's perceived functional status of health

In a follow-up [19 months (range 3-30)] study by Duggan and her co-workers from 1994, there were 38 patients with CLI and age 65 years or older who had undergone surgical revascularization. (The perioperative mortality rate was 5.2% and 2-year survival was 61%, and the rate of limb loss over that period was 27%, 5.5% early limb loss.) There was no statistically significant difference in health perceptions (the Rand scores) between patients with successful limb salvage and patients with failed bypass grafts requiring amputation. There was no difference between patients with successful bypasses and patients with failed bypasses in the amount of pain reported- amputation being an effective pain control measure. That might have been explained by comorbid conditions that continue to deteriorate in spite of limb salvage interventions. The authors suggest that it is possible that addressing rehabilitation issues earlier in the care of these patients may produce a more positive outcome. Patients who have had strokes or debilitating arthritis may lose substantial functional ability during convalescence from peripheral bypass surgery, which may take weeks to heal, especially when associated with gangrene or ulceration and that is why the functional outcome goals need to be better defined for patients who need limb salvage vascular operations to enhance the quality of care given these patients and to be in concert with emerging health policy. (Duggan et al., 1994)

Feinglass and his co-workers have reported on a prospective 18-month study of 526 patients with intermittent claudication, with an 18 months follow-up. There were 44 who had undergone endovascular, 60 who had undergone surgical LERs, 277 medically treated unmatched patients, and a 145 younger, most closely at baseline matched, and more disabled, medically treated patients' subgroup. By MOS SF-36, physical functioning improved by 17% with the surgically treated and 14% with the endovascularily treated patients, 28% and 27% less bodily pain and 18% and 13% less leg symptoms, respectively. The ABI improved by 0.20 with the surgically treated and by 0.09 with the endovascularily treated patients. The 277 medically managed unmatched group had a decline on these MOS SF-36 scores, but among the medically treated matched subgroup there was a 5% improvement in walking distance. (Figure 4) (Feinglass et al., 2000a)

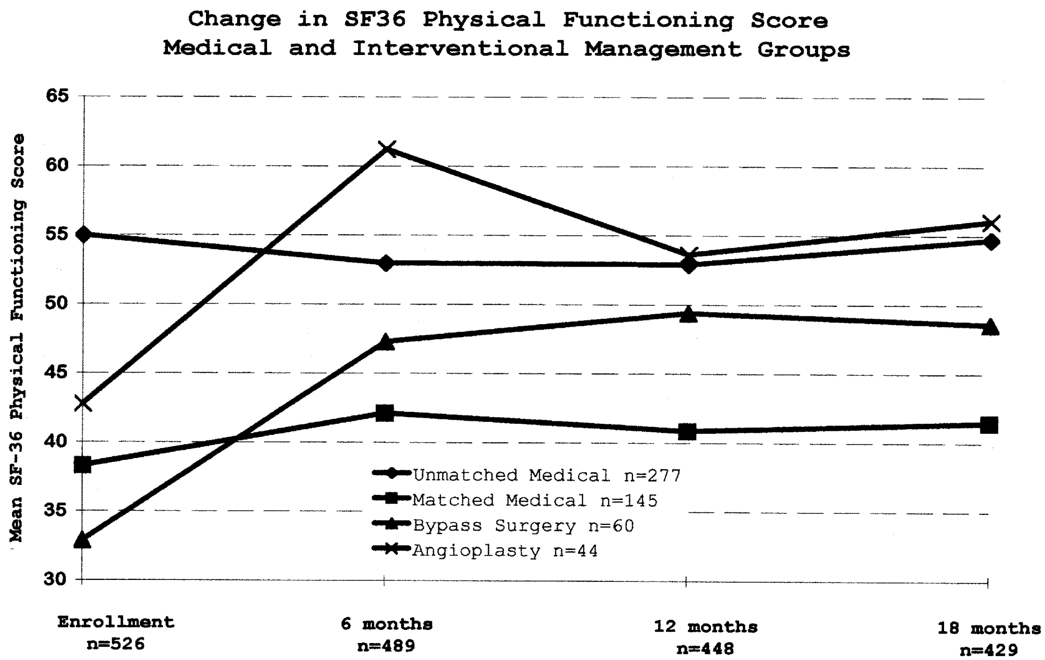

Figure 4. Change in MOS SF-36 PF scores over 18 months (Feinglass et al., 2000a) Reproduced with the permission of the copyright holder.

Based on Figure 4, it seems as if the heterogeneity of the whole treated group (n=526) is affecting the long term MOS SF-36 PF results. There is a risk of bias formed by a survival cohort; it is questionable how much the groups differ from each other in the enrollment and in different measurement points of the follow-up.

2.6.3 Expressed as patient's perceived psychosocial status of health

Patients' perceptions of the result of LEA vary widely, yet the factors associated with this variability are not well understood (Pinzur et al., 1992). Matsen and her co-workers found that the patient's perceived result of amputation does not associate with the amount of the limb that is amputated but rather with factors that may be optimized by surgical, prosthetic, and social management: (1) the comfort of the residual limb; (2) the condition of the contralateral limb; (3) the comfort, function, and appearance of the prosthesis; (4) social factors; and (5) the ability to exercise recreationally, but the level and laterality of the amputation do not correlate with the patients' perceptions. (Matsen et al., 2000)

Hanley and her co-workers' findings from 2004 support a biopsychosocial model of long-term adjustment to amputation and phantom limb pain (PLP). In addition, results suggest that some psychosocial variables are more important than others for predicting adjustment, providing important implications for early interventions after amputation. They followed 70 amputees' PLP intensity, cognitions (catastrophizing, perceived control over pain), coping (pain-contingent rest), social environment (social support, solicitous responding), and functioning (pain interference, depressive symptoms) for two years. Depressive symptoms and pain interference changed significantly in one year and in two year post amputation measurements. Catastrophizing and social support were associated with improvement in both criterion measures, while solicitous responding was associated with worsening in both measures. (Hanley et al., 2004)

By using the Center for Epidemiologic Study Depression Scale the prevalence of depressive symptoms among persons with limb loss, in general, is 29%. Risk factors for depressive symptoms include being divorced, being somewhat bothered with back pain or phantom limb pain, and having residual limb pain among persons aged 18 to 54. Having higher education is a buffer against depressive symptoms. (Darnall et al., 2005)

Social discomfort is a predictor of depression among amputees (Rybarczyk et al., 1992) Individual coping styles are important predictors of psychosocial adaption to e.g. amputation. Avoidance is strongly associated with psychosocial distress and poor adjustment. In contrast, problem solving type of coping is negatively associated with depressive and anxious symptomatology whereas seeking social support is negatively associated with depressive symptoms and positively associated with social adaption. (Desmond and MacLachlan, 2006)

2.7. Summary

Despite marked advances in the technical ability to perform LER, the decision whether to perform primary amputation or attempt revascularization in high risk patients is a major part of modern vascular care. With an aging population and improved medical care that has increased life expectancy, more patients with severe systemic disease are presenting with CLI. In addition, it is well recognized that CLI patients suffer diagnostic delays and poor risk factor modification (Bradley and Kirker, 2006), which in part contributes to limb loss and poor patient survival (Nehler and Peyton, 2004). Diabetic and uremic patients are at high risk for both leg and life loss after LER (Biancari et al., 2000; Subramaniam et al., 2005).

Patient's status of health is worth evaluating properly in order to plan the postintervention rehabilitation. A functional performance measure 6 MW, which can be administered in an office setting, predicts mortality in persons with PAD beyond that provided by the ABI (McDermott et al., 2008). The patient's own perception of his or her physical functioning and possible depressive symptoms are important factors that well predict also the outcome after LER or LEA (Cherr et al., 2007). Depressed mood may either precede mobility limitation or follow from mobility limitation (Hirvensalo et al., 2007). Pain, commonly seen in LER or major LEA patients, may be an underlying factor in both depressed mood and mobility limitation.

3. AIMS OF THE STUDY

The study aims were to evaluate the survival, the functional capacity and the quality of life of patients with severe peripheral arterial disease, and the special aims were:

1. To assess the incidence of major lower extremity amputations, the reamputations, and the survival of major lower extremity amputees (I).
2. To assess functional capacity in patients after major lower extremity amputation (II).
3. To assess quality of life after lower extremity revascularization (IV) and major amputation (III).
4. To evaluate how the health care organization is able to fulfill the needs of patients with severe PAD (I-IV).

4. MATERIALS AND METHODS

4.1. Study designs and settings

Studies I and II were retrospective from 1998 to 2002 and the patients were followed until the end of 2006. The studies were based on hospital records. The setting was Turku, Finland; the amputations were performed at Turku City Hospital and at Turku University Hospital. The population of Turku was 174 868 on December 31, 2005, and the total population of Finland at that time was 5.3 million.

In studies III and IV the study design was observationally retrospective and cross sectional. They were questionnaire studies, where a case-control methodology in comparisons between major LEA patients and age-, gender- and domicile-matched controls in study III, and between LER patients and similarly matched controls, in study IV, was applied. These studies were also conducted in Turku, Finland. All major LEAs were performed in 1998-2002. The amputees were interviewed using a set of questionnaires in 2004-2006. Their controls postal questionnaire intervention was performed in 2005-2006. The LER interventions for the study IV patient population were performed between 1998 and 2003; and LER patient population's postal questionnaire intervention was made in 2004 and their controls postal inquiry in 2005-2006. The questionnaire is seen in Appendix 1.

4.2. Study populations

The study patient population consisted of two groups: 1) All patients who had undergone their first major LEA due to PAD, in 1998-2002 (studies I, II and III) and 2) all those who had undergone either one or several endovascular only and/or surgical LERs, but not major LEA in 1998-2003 (study IV).

4.2.1 Patients with major lower extremity amputation in studies I, II and III

From 1998 to 2002, 210 patients (mean age 76.6, SD 10.7 years, 45% men) underwent index major LEA because of PAD. The operations were performed at Turku City Hospital on 184 patients and at Turku University Hospital on 26 patients. A hundred and thirty-eight of them had had a primary LEA, 34 had had prior endovascular LERs only, 32 prior surgical LERs only, and 15 had both endovascular and surgical LERs before their first major LEA.

4.2.1.2 Patients in study II

In study II, 149 of the 210 amputees were admitted from home for the intervention. Thirty (20%) of them died within the first 31 days after the first major LEA, and were excluded.

The remaining 119 amputees formed the material for that part of the 2nd study where predictors for the institutionalization were analyzed.

4.2.1.3 Patients and controls in study III

Of the 210 amputees, 61 (29%) were alive during spring 2004. Fifty nine of them were available for interview for the study. Each of them had two age-, gender- and domicile matched controls. (Figure 5)

The controls were recruited as follows: In order to get two age- and gender-matched controls for each amputee, six age- and gender-matched controls were chosen at random from Turku citizens using the Population Register Centre of Finland for each patient. Inquiries inviting participation, as a postal survey only, were initially sent to the first two names on the list, and then if an answer was not obtained within 2 to 3 weeks the next two on the list were contacted. The controls' age was within +/- one year of the patients' age.

Drop-outs of study III

The fact that there were eight major LEA amputated patients having had their index major LEA in 1998-2002 was found in spring 2006 and for that reason one amputee interview was missed; the patient had died earlier that year. Besides, another amputee was unreachable.

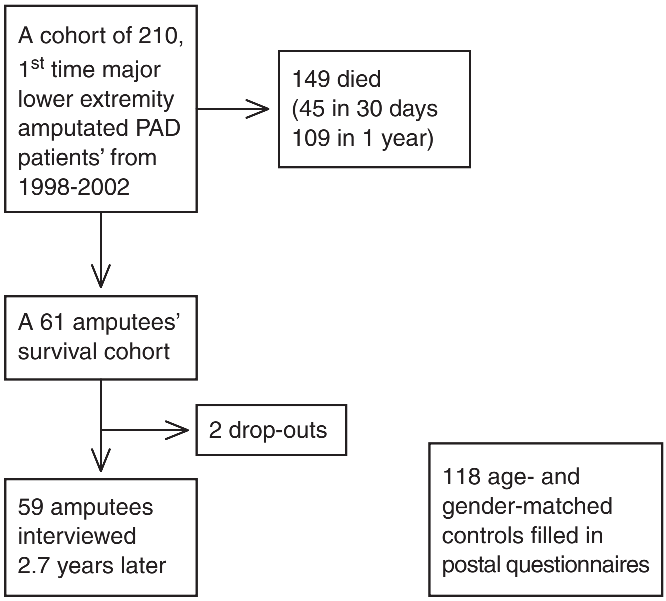

Figure 5. Study III participants' flow chart

4.2.1.4 Patients and controls in study IV

PAD patients who had undergone endovascular and/or surgical LERs were taken from the Finnish National Hospital Discharge Register (HILMO). All revascularizations had been carried out at the Turku University hospital. Indications for them were as follows: 1) walking distance before claudication symptoms occurred ≤ 300 meters, and/or 2) in the la Fontaine classification all patients were at least in class II (e.g. intermittent claudication, daily rest pain, focal tissue necrosis) (Fontaine et al., 1954). In total, 519 Turku citizens had undergone one or more endovascular LERs (with codes PE1AT and/or PE1BT, NOMESCO, 2002) and/or surgical LERs at the inguinal, femoropopliteal, or infrapopliteal levels in 1998-2003. One hundred and thirty one endovascular LER patients and a hundred surgical LER patients returned written consents and completed questionnaires, and formed the patient data of this study (Figure 6). The mean time between the last revascularization and the questionnaire response was 2.7 years, SD 1.3 yrs (range 0.6–5.4 years) for the endovascular patients, and 3.5 years, SD 1.8 years (range 0.3–6.4 years) for the surgical LER patients.

The controls were recruited the same way for the PAD patients as for the amputees, but one for each participating patient.

Drop-outs of study IV

There were 288 drop-outs from the study: 1) Ninety-eight (98/519, 19%) patients did not respond in 2004. 2) Forty (40/519, 8%) were alive during the data collection in 2004, but had had a major LEA. Seventeen of these 40 patients had undergone PTAs, and 23 patients had undergone surgical LERs. 3) One hundred and fifty (150/519, 29%) patients had died before the data collection in 2004. Of this group, 80 patients had undergone endovascular LERs, of whom 28 (28/80, 35%) had had a major LEA before their death, and 70 patients had undergone surgical LERs, of whom a further 24 (24/80, 34%) had had a major LEA. (Figure 6)

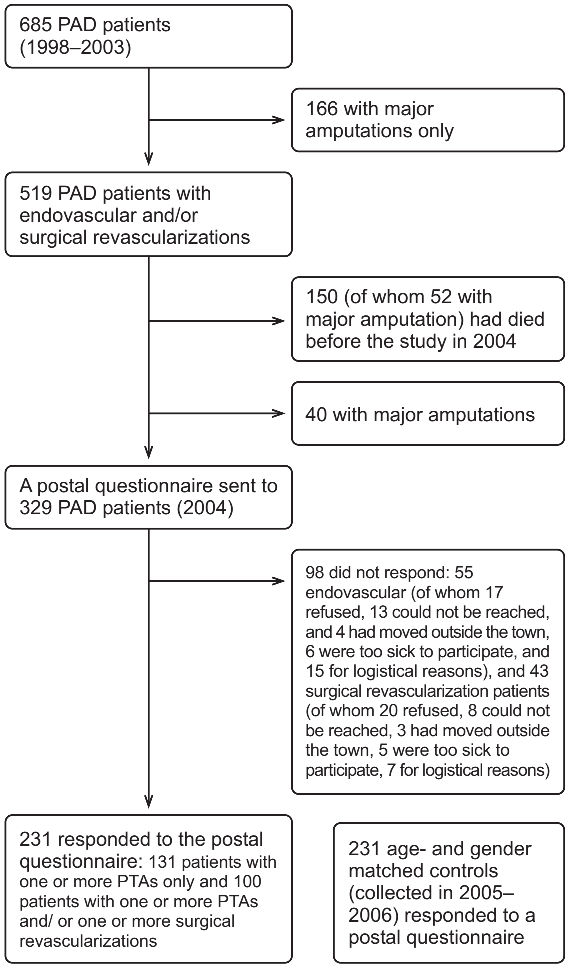

Figure 6. Flow chart for peripheral arterial disease (PAD) patients in 1998-2003 in the City of Turku, Finland.

4.3. Data collection

Data collection started in 2003 and finished up with the last causes of death check in 2008.

4.3.1 Amputated patients and review of their medical records for studies I and II

The hospital register systems of Turku City Hospital and Turku University Hospital were used, and all medical records with codes (NOMESCO, 2002) of major LEAs: 1) above-knee amputations (AKA): hip disarticulation (code NFQ10, or transfemoral amputation (NFQ20) , and 2) below-knee amputations (BKA): through-knee (NGQ10) or transtibial amputation (NGQ20), were reviewed. There were 221 AKAs, 3 hip disarticulations and 75 BKAs on 210 patients. The numbers of these same codes were also requested from the register maintained by THL (National Research and Development Centre for Welfare and Health), Finland, where all operations are to be reported. This was done to recheck the number of amputees during the study period. The THL register matched up with the number of all major LEAs, including reamputations, and the number of amputations done for reasons other than PAD. The medical records of the patients who had only minor LEAs, i.e. below-ankle joint amputations or at the talocrural level of LEA (NHQ10) were not requested. The dates and immediate and basic causes of death were obtained from Statistics Finland (http://www.stat.fi/index.html).

4.3.1.1 Exclusion criteria

Patients with vasculitis (n=3) and Buerger's disease (n=1) were excluded from the series. In addition, there were 20 persons with PAD who had had their first major LEA, and three of them even had their second major LEA, done in 1977-1997, and they were therefore excluded. Nine patients who underwent a major LEA due to reasons other than vascular pathology were excluded. One major LEA was due to metastases of kidney cancer, five were due to trauma, and one alcoholic lost his legs due to hypothermic injury, while two patients had rheumatoid arthritis and lost their legs due to infectious knee endoprosthesis.

4.3.2 Postal questionnaire data collection

The data for studies III and IV were collected by means of postal questionnaires.

In order to check how the questionnaire worked in practice, the author pilot-tested it by means of four interviews. Prior to the start up of the project, as well as during collection of the material, the author gave detailed directions to the nurses, pertaining to how the nurses and the author were to conduct the interviews.

For the institutionalized patients (n=30), the author did 27 (90%) of the interviews and the public health nurses 3 (10%), and for the home-dwelling patients (n=29), the author undertook 23 (80%) of the interviews, and the public health nurses 6 (20%).

All 118 controls for the amputees and 231 for the revascularized PAD patients returned, by mail, written consent and self-administered questionnaire. The same questionnaire was used for interviewing the amputees. The responses of those 165 revascularized PAD patients who took part in the ABI measurement and MMSE test were rechecked by the author together with the patients. Those patients' medication was rechecked at the same time from their electronic medical records.

Close relatives of some elderly revascularized patients and controls contacted the author and explained that they would help their parent to complete the questionnaire. This was permitted.

4.3.3 Ankle-brachial pressure index

In order to evaluate the severity of PAD a trained research nurse measured the resting ABI by Doppler of the 165 PAD patients willing to be tested.

4.3.4 Mini-Mental-State Examination

A trained research assistant, a medical student performed MMSEs on 172/231 (74%) patients, (7 of whom had had their MMSE monitored during an interview made for diabetic home-care patients). MMSE sum scores of 24-30 were considered indicative of no cognitive impairment, 18-23 of mild and 0-17 of severe cognitive impairment (Tombaugh and McIntyre, 1992). According to MMSEs, most had no cognitive impairment.

4.4. Outcomes

In study I: Population-based incidence rates of index amputations, mortality and standardized mortality ratio (SMR).

In study II: The main outcome measure was institutionalization in a sample of older persons with recent major LEA, and the secondary outcome measures were prosthesis use and ambulation recovery.

In studies III and IV: Quality of life assessed with the 15D health-related QoL instrument, the Rand-36 *Physical Functioning*- and *General Health* subscales, the Geriatric Depression Scale, the 6-item Brief Social Support Questionnaire, the Self-reported Life Satisfaction score, and one 'Perceived State of Health' question.

Quality of life and status of health measures

The 15D health-related QoL instrument (15D HRQoL) (Sintonen, 2001), which is a Finnish generic HRQoL scale, the number score of the 6-item Brief Social Support Questionnaire (SSQ6N) (Sarason, 1987) to assess perceived social support, Rand-36 *Physical Functioning* subscale (Rand-36 PF**)** (Aalto, 1999; Hays et al., 1993) as a physical/mobility screening scale, Geriatric Depression Scale GDS) (Yesavage et al., 1982) to find out depressive symptoms, and the Life Satisfaction score (LS) (Allardt, 1973; Koivumaa-Honkanen et al., 2000) were used to triangulate the health-related quality of life as a whole. The 'perceived state of health' was obtained by asking whether participants felt their state of health to be 'good', 'quite good', 'fair', 'rather poor' and 'poor'. QoL and status of health measures used are presented in more detail in the Appendix 2.

In study III, the respondents' compliance in completing the questionnaire was good; a high number of patients' responses allowed a good number of case-control pairs or stratums (98% in 15D HRQoL, 93% in SSQ6N, 98% in the 10 items of Rand-36 PF, 97% in the 4 items of Rand-36 GH, 95% in GDS, 97% in LS, and 100% in the question of 'perceived state of health') into the analyses. In study IV, the respondents exhibited excellent compliance in completing the questionnaire; a high number of patients' responses allowed a large number of case-control pairs or stratums (99% in 15D HRQoL, 97% in SSQ6N, 95-99% in the 10 items of Rand-36 PF, 99% in GDS, 100% in LS, and 99% in the 'perceived state of health' question of) into the analyses.

4.5. Explanatory variables

In analysis and statistical models, comorbidity, final level of amputation, reamputation, revascularization, medication, and sociodemographics were used as explanatory variables to explain the outcomes.

4.5.1 Comorbidity

The diseases shown in the medical records were coded according to the Finnish version of International Statistical Classification of Diseases and Related Health Problems (ICD10). Those who had ICD-10 diagnoses of dementia, i.e. F00, F01, F03 or G30, and those who were found to score 0-17 points in the MMSE (Folstein et al., 1975; Tombaugh and McIntyre, 1992) were categorized as having cognitive impairment comorbidity. Diabetes was coded for those who had ICD-10 diagnostic codes of E10-E11 or had diabetes medication in their records.

4.5.2 Final level of amputation

The dates and the levels of all amputations were collected to determine the final level of amputation.

4.5.3 Reamputation

All major LEAs performed after index major LEA were defined as major, i.e. above the ankle, reamputations. Therefore, the dates and the levels of all subsequent amputations were collected to determine the reamputations: ipsilateral as to the index major amputation at the same level, from below to above knee, and as well contralateral major amputations. This also included revisions, providing the procedures were recorded in the medical records as transfemoral amputations (NFQ20), hip disarticulations (NFQ10), or transtibial amputations (NGQ20). Minor amputations, which were toe and transmetatarsal amputations, were also collected.

4.5.4 Revascularization

Previous revascularizations were collected as follows: percutaneous transluminal angioplasty: codes (NOMESCO, 2002) PE1AT and PE1BT, and vascular reconstructions: Y-prosthesis, bypass from the infrarenal abdominal aorta and iliac arteries: codes (NOMESCO, 2002) PDH50, PDH51, PDH52, and PDH54, bypass from a femoral artery and branches: PEH56 and PEH57, bypass from axillary to bilateral femoral arteries: PGH44, bypass from a femoral to the contralateral femoral artery: PGH47, bypass from a femoral artery to infrapopliteal arteries and from a popliteal artery to arteries of the lower leg and foot: PFH58, PFH59, PFH62, PFH63, PFH64, PFH66, and PFH67.

4.5.5 Medication

The preamputation medication, medication at the time of the interviews and postal inquiry was coded according to the Guidelines for the Anatomical Therapeutic Chemical classification system (2003).

4.5.6 Sociodemographics

Socio-demographic variables, health behavior, and health status information were gathered from the patient records. Smoking habits and MMSE, if available, were obtained from medical records for studies I and II.

Background data in the questionnaire studies III and IV consisted of basic demographics, including smoking habits, alcohol consumption, present medical diagnoses, cardiac symptoms and current medication. Body mass index (BMI) calculated as self-reported current weight in kilograms divided by self-reported square of height in meters. Both the Weighted Index of Comorbidity (Charlson Index) and the age-related risk were calculated according to the model described by Charlson (Charlson et al., 1987; Sundararajan et al., 2004).

4.6. Other, mainly descriptive variables

4.6.1 Indications for amputation

Indications for amputation, including chronic critical ischemia, gangrene (arterial ulcer and rest pain), osteitis, or acute limb ischemia, and the sides of amputations were also collected.

4.6.2 Prosthesis usage

In 1998-2002, routine care for an amputated patient was as follows: The patient was moved from the surgical ward into the geriatric rehabilitation unit of Turku City Hospital in the days following the amputation. There each amputee was assessed by a multidisciplinary team consisting of a specialist in geriatric medicine, physiotherapist, occupational therapist, and specialist in prosthetics. This team selected those whose recovery seemed to proceed well enough for further prosthesis use. During the patients' convalescence pressure trials for the stump were given, and a rehabilitation prosthesis was used as soon as the healing stump allowed. After the patient had been discharged either home or to institutional care he or she continued to come to the prosthesis users' training group twice a week. The training group of amputees was collected from their residences by taxi and also returned home by taxi supported by the city medical care.

The mobility and rehabilitation capabilities of the training group amputees were reviewed from the rehabilitation unit's records. Furthermore, the physiotherapist of the training group was interviewed. The manner the patients were able to use their prostheses was classified by a physiotherapist according to the classification system devised by Narang and his co-workers (Narang et al., 1984; Pohjolainen et al., 1990). In this classification, class I means ambulating with prosthesis and without any other walking aids outdoors and indoors, class II means ambulating with prosthesis indoors, but requiring one walking stick or crutch for outdoor activities, class III means independent indoors, ambulating with prosthesis and one crutch indoors, but requiring two crutches outdoors and occasionally a wheelchair , class IV means walking indoors with a prosthesis and two crutches or a walker, but requiring a wheelchair for outdoor activities, class V means walking indoors only short distances, but primarily a wheelchair user. The classification also includes classes VI and VII (class VI walking with aids, but without prosthesis, and class VII ambulates by a wheelchair). However, codes VI and VII were not found in the medical records.

4.7. Statistical analyses

All statistical analyses were carried out using SAS/STAT® software, Version 9.1.3 SP3 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). P-values less than 0.05 were considered to be significant.

In Study I: The follow-up (measured in days and expressed as years and person-years) started on the date of the index major amputation and continued until death or the end of the study period, December 31, 2006. Population-based incidence rates of index LEAs were calculated separately for each year of 1998-2002. The incidence rates of index amputations were calculated separately and combined, for both genders and the age groups of younger than 65 years, 65-74, 75-84, and 85 years and older. All incidence rates were standardized for age and gender with the direct method, using the December 31, 2005 population of Finland as reference. Therefore, these standardized incidence rates can be compared to the overall amputation rates in Finland or some other district or city with a population composition similar to that in Finland. Incidence rates are reported per 100 000 person-years.

Comparisons between men and women were made with the Chi-Square Test and Fisher's Exact Test when analyzing categorical variables. Wilcoxon's rank sum test was used to compare differences in age (continuous variable) between men and women, due to the skewness of the age distribution. The follow-up time for survival analysis was calculated from the date of the first major amputation to death or the end of the study period. Survival curves were calculated with the Kaplan-Meier method. The potential predictors for survival were first analyzed with age- and gender-adjusted Cox proportional hazards models. The significant predictors obtained from these analyses were included in the multivariate Cox models. The results were quantified by HR and their 95% confidence intervals (CI).

The standardized mortality ratio (SMR) was calculated as the ratio of the number of deaths in the study group to the mortality that would be expected in the Turku population (Last, 2001).

In Study II: The sociodemographic factors, comorbidities, and preamputation medications of the 119 amputees were cross-tabulated by discharge destination; home or institutional care, and tested using the Chi-Square Test or Fisher's Exact Test. Sociodemographic and comorbidity variables having p-values of less than 0.05 and the preamputation medication variables having p-values less than 0.10 were selected (Fletcher, 2005) for the logistic regression analysis.

Discharge destination was a dependent variable in the logistic regression models. Predictors for discharge destination were first analyzed by univariate analysis. In the second phase, age- and gender-adjusted analyses were carried out. Lastly, significant predictors in the age- and gender-adjusted analyses were included in the final multivariate logistic model. Associations were quantified by odds ratios (OR) and their 95% CIs.

In Study III: The differences in categorical variables between amputees and their age and gender matched controls were analyzed with logistic regression using generalized estimating equations to account for matching. Binary logistic models were revealed for dichotomic dependent variables and cumulative logistic models for ordinal dependent variables. The results of logistic regression were quantified by calculating OR and cumulative odds ratios (COR) with their 95% CI. The continuous variables measuring quality of life (15D HRQoL-, Rand-36 PF-, GDS-, Rand-36 GH-, SSQ6N-, LS scores), the number of self-reported diagnoses, the Weighted Index of Comorbidity and the Charlson Combined Comorbidity Index were compared between amputees and their age- and gender-matched controls using a linear mixed model where stratum (one amputee and his/her two controls) was used as a random effect. GDS-, LS score and mean number of self-reported diagnoses were logarithmically transformed, and the SSQ6N score was square root transformed for statistical analyses due to skewed distributions. 15D dimensions of health were compared between amputees and their controls using a stratified Mann-Whitney U-test. The Chi-Square Test or Fisher's Exact Test was used to compare categorical background data between amputees living at home or in institutional care.

The differences in QoL scores between amputees with and without prosthesis, and those who lived at home and those who lived in institutional care were analyzed using analysis of covariance with adjustment for age.

In Study IV: The differences in categorical variables between PAD patients and their age- and gender-matched controls were analyzed with logistic regression using generalized estimating equations to account for matching. Binary logistic models were revealed for dichotomic dependent variables and cumulative logistic models for ordinal dependent variables. The results of logistic regression were quantified by calculating OR and COR with their 95% CI. Continuous background variables between PAD patients and their controls were compared using paired t-test. The 15 dimensions HRQoL were compared between PAD patients and their controls using

Wilcoxon Signed Rank test. Chi-Square Test or Fisher's Exact Test was used to compare categorical background data between endovascular and surgical revascularization patients. Continuous background variables between these patients were compared using two-sample t-test.

Explanatory variables (both background variables and the QoL scale values) for 'perceived state of health' were separately analyzed for the PAD patients and the control group by the cumulative logistic regression model.

4.8. Ethical considerations

Written consent was obtained from the interviewed amputees, participating revascularized PAD patients, and all controls. The Joint Ethics Committee of Turku University and the Hospital District of Southwest Finland approved the research plan. Finland's Ministry of Social Affairs and Health approved the study plan and granted the access to registers.

5. RESULTS

5.1. Background medical record data of the patients in studies I-III

Of patients younger than 65 years, 62% returned home. Half of the patients had diabetes (104/210, 50%), (type 1: 6.7% and type 2: 93.3%), whereas 72% of the under 65-year-olds had diabetes. All type 1 diabetics had nephropathy. Basic characteristics of the amputated group are presented in Table 8.

Table 8 Sociodemographic and other background data of the 210 amputees

Characteristic	Men (N=95)		Women (N=115)		p-value
	n	%	n	%	
Age group[2]					<0.001[1]
<65	22	23.2	7	6.1	
65-74	22	23.2	22	19.1	
75-84	39	41.0	51	44.4	
≥85	12	12.6	35	30.4	
Mean age (SD), yrs	73.1(11.0)		79.5(9.6)		<0.001[3]
Marital status[4]					<0.001[1]
Married or cohabitation	51	54.3	19	16.7	
Widowed	21	22.3	64	56.1	
Unmarried	11	11.7	17	14.9	
Divorced	11	11.7	14	12.3	
Vocational education[5]					<0.001[1]
No vocational education	50	53.2	97	84.3	
Vocational school or learning at work	35	37.2	10	8.7	
College or university	9	9.6	8	7.0	
Smoking[6]					<0.001[1]
Non-smokers	32	43.2	52	80.0	
Ex-smokers	10	13.6	2	3.1	
Current smokers	32	43.2	11	16.9	
Admitted from					0.150[1]
Home	73	76.8	76	66.1	
Intermediate care	13	13.7	18	15.6	
Long-term care	9	9.5	21	18.3	
Discharged to					0.037[1]
Home	31	32.6	20	17.4	
Intermediate care	9	9.4	14	12.2	
Long-term care or stayed in hospital	55	58.0	81	70.4	

[1]Chi-Square test; [2]In years by the time of the first amputation done for the person; [3]Wilcoxon rank sum test; [4]Missing data=2; [5]Missing data=1; [6]Missing data=71

5.2. Background of the patients and their controls in study IV

Males were over represented in the patients. Age- and gender-matched controls were more commonly non-smokers and/or married or living with a companion than the patients. Patients had less vocational education, lower BMI, more commonly cardiac symptoms, more self-reported diseases and both their Weighted Index of Comorbidity/ Charlson Index and the Charlson Combined Comorbidity Index were higher, when compared with their controls (Table 9). Patients, who had undergone surgical revascularization were younger than PTA patients, more commonly had vocational education, and used sedatives more frequently.

Both endovascular and surgical LER patients had low ABIs (0.5–0.89 in 96/165, 58%). According to MMSEs, most had no cognitive impairment.

Table 9 Differences between peripheral arterial disease (PAD) patients and their age- and gender-matched controls. A cross-tabulation and a logistic regression model.

Variable	PAD patients N=231 (%)	Controls N=231 (%)	p-value[2]	Univariate analysis[1] OR[3] (95% CI[4])
Mean age, yrs (SD[3], range)	69.5 (10.5, 39-91)	69.5 (10.5, 39-90)		
Age				
<75	147 (64)	147 (64)		
≥75	84 (36)	84 (36)	-	
Gender				
Men	138 (60)	138 (60)		
Women	93 (40)	93 (40)	-	
Marital status				
Married or cohabiting	114 (49)	162 (71)		1
Widowed, divorced or unmarried	117 (51)	67 (29)	**<0.001**	2.48 (1.74-3.55)
Residence				
Home	220 (95)	225 (97)		1
Intermediate care	10 (4)	6 (3)		
Long term care	1 (1)	0 (0)	0.200	1.88[6] (0.72-4.94)
Vocational education				
College or university	30 (14)	55 (26)		1
Vocational school or learning at work	78 (36)	91(44)		
No vocational education	111 (51)	62 (30)	**<0.001**	2.45[6] (1.71-3.50)
Smoking habits				
Non-smoker	44 (19)	119 (53)		1
Ex-smoker	114 (49)	87 (39)		
Current smoker	73 (32)	20 (9)	**<0.001**	4.79[6] (3.45-6.66)
Mean BMI[7]; (SD[3], range)	25.9 (4.4, 16.5-42.3)	27.2 (4.6, 15.6-50.4)	**0.004**[8]	
Alcohol consumption				
No/Light	96 (42)	82 (36)		1
Average	124 (54)	137 (59)		
Heavy	9 (4)	11 (5)	0.227	0.80[6] (0.56-1.15)
Mean number of self-reported diseases (SD[3], range)	3.8 (1.8, 1-12)	1.8 (1.6, 0-7)	**<0.001**[8]	
Mean value of the Charlson Index (SD[3], range)[9]	0.69 (1.00, 0-6)	0.42 (0.78, 0-4)	**<0.001**[8]	
Mean value of Charlson Combined Comorbidity Index (SD[3], range)[10]	3.19 (1.51, 0-7)	2.93 (1.42, 0-8)	**0.002**	
Heart disease[11,12]	98 (42)	48 (21)	**<0.001**	2.81(1.91-4.13)
Hypertension[11,13]	101 (44)	74 (32)	**0.008**	1.65 (1.14-2.38)
Diabetes[11,14]	69 (30)	28 (12)	**<0.001**	3.09 (1.95-4.89)
Depression[11,15]	12 (5)	3 (1)	**0.031**	4.16 (1.14-15.16)
Cardiac symptoms[16]				
Palpitation without physical exercise	143 (62)	107 (47)	**<0.001**	1.94 (1.11-2.32)
Irregular heartbeats	132 (58)	109 (48)	**0.013**	1.60 (1.07-2.30)
Chest pain during anger or other kind of emotion	118 (52)	72 (32)	**<0.001**	2.33 (1.58-3.42)

Medication, (ATC[17]) [18]				
Psychopharmaceuticals				
Psycholeptics, N05	75 (32)	25 (11)	**<0.001**	3.96 (2.46-6.39)
Sedatives, N05C	54 (23)	17 (7)	**<0.001**	3.84 (2.19-6.93)
Psychoanaleptics, N06	34 (15)	12 (5)	**0.001**	3.15 (1.59-6.23)
Serum lipid-reducing agents, C10	119 (52)	57 (25)	**<0.001**	3.24 (2.18-4.82)
Beta blocking agents, C07	94 (41)	65 (28)	**0.003**	1.75 (1.20-2.55)
Agents acting on the renin-angiotensin system, C09	98 (42)	66 (29)	**0.002**	1.84 (1.26-2.69)
Antiplatelet drugs, aspirin, clopidogrel, dipyridamol, B01AC04,06,07	150 (65)	65 (28)	**<0.001**	4.73 (3.19-7.10)

[1]Logistic regression using generalized estimating equations to account for age- and gender-matching
[2]<0.05 is considered as significant
[3]Odds ratio
[4]Confidence interval
[5]Standard deviation
[6]Cumulative odds ratio; worse categories compared to better categories
[7]Body mass index
[8]Paired t-test; values were log-transformed for statistical analysis
[9]The Charlson Index covers major disease categories weighted according to their prognostic impact on patient survival
[10]Weighted Index of Comorbidity + age-related risk
[11]An answer 'no' in each disease is a reference group
[12]ICD10 (International Classification of Diseases, 10th version) codes I11-I51, Z45, Z95
[13]in ICD10 codes I10-I11
[14]in ICD10 codes E10-E11
[15]in ICD10 codes F32-F34
[16]'No cardiac symptoms' is a reference group
[17] Anatomical Therapeutic Chemical classification system in Guidelines for ATC classification and DDD assignment, 2003
[18]No medication' is a reference group

5.3. Study I

5.3.1 Incidence rates of amputation

The overall age- and gender-standardized incidence rate of Ak and BK amputations during 1998-2002 was 24.1/100 000 person-years, 24.9 for men and 23.3 for women. The annual age- and gender-standardized incidence rates were 27.1, 24.2, 26.6, 23.2, and 19.5/ 100 000 person-years in 1998, 1999, 2000, 2001, and 2002, respectively (Figure 7).

Figure 7. Incidence rates of major lower extremity index amputations per 100 000 person-years by gender, in Turku, Finland. The figures have been standardized for age and gender, by using the direct standardization method to the December 31, 2005 population of Finland.

5.3.2 Amputation indications

The amputation was performed due to chronic critical ischemia, with gangrene or arterial ulcer in 256 cases; osteitis in 20 cases (16 among diabetics, and hence only 4 among patients with other diagnoses); and acute limb ischemia in 23 cases.

5.3.3 Mortality and its predictors

The Kaplan-Meier curve for the survival of the 210 amputees is shown in Figure 8. The one-month mortality rate was 21%, one-year rate 52%, and overall mortality rate 80%. The mean annual mortality risk of the age- and gender-matched population of Turku was approximately 7%. The SMR was 7.4, i.e., when comparing the first-year mortality risk of amputees, lower extremity amputations were associated with a 7.4-fold annual mortality risk compared with the reference population in Turku.

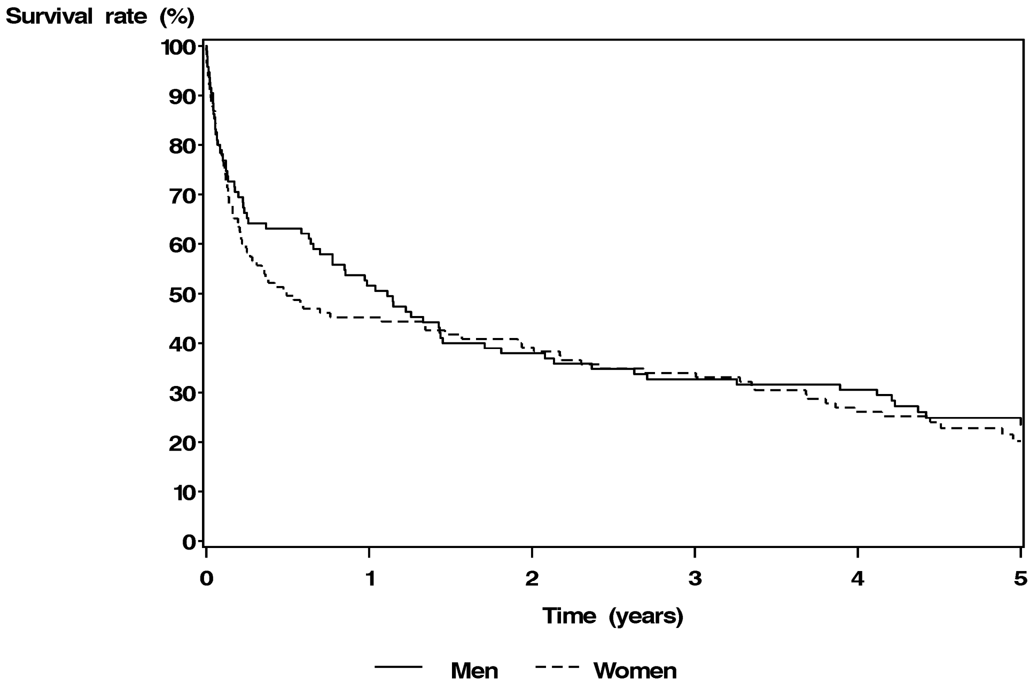

Figure 8. Kaplan-Meier survival curve for the 210 major lower extremity amputees, for men and women separately.

Cardiovascular diseases predicted similarly the 31-day, one-year and overall mortality rates in age- and gender-adjusted analysis. Multiple comorbidities (p=0.023) and unilateral AK amputations (p=0.047) were significant predictors of overall mortality in age- and gender-adjusted analysis. Cardiovascular diseases remained a significant predictor of 31-day and overall mortality in multivariate analysis (p=0.008 and p=0.015, respectively). Bilateral (BK/BK and AK/BK) amputations (p=0.009 and p=0.023, respectively) were significant predictors of 31-day mortality in both age- and gender-adjusted and multivariate analyses.

5.3.4 Reamputations

During the follow-up period (from January 1, 1998 to December 31, 2006), 66% of the patients (138/210) underwent only one amputation. The figure of the trajectories of the 210 amputees, in Appendix 3, shows amputees' exposure to reamputations, prosthesis use, and deaths. As far as the age is concerned, of the 22 men under 65, 13 (58%) had had only one amputation, whereas the corresponding number of women under 65 years old was 3 (43%). Table 10 shows the laterality of major reamputations performed to the patients.

Table 10 Amputations of 210 patients with peripheral arterial disease

Number of amputations	Men (N=95)	%	Women (N=115)	%	p-value
One amputation					<0.001[1]
unilateral below-knee	22	36.1	7	9.1	
unilateral above-knee	38	62.3	68	88.3	
bilateral above-knee	1	1.6	2	2.6	
Two amputations					
bilateral below-knee	2	5.9	5	13.2	
bilateral above-knee	11	32.3	11	29.0	
above-knee and contralateral below-knee	2	5.9	4	10.5	
ipsilateral above-knee to above-knee	**6**	**17.7**	**4**	**10.5**	
ipsilateral below-knee to above-knee	***8***	***23.5***	***4***	***10.5***	
Three amputations					
ipsilateral above-knee and contralateral above-knee amputation	**1**	**2.9**	**2**	**5.3**	
ipsilateral below-knee to above-knee and contralateral above-knee amputation	***2***	***5.9***	***6***	***15.8***	
ipsilateral below-knee to below-knee and contralateral above-knee amputation	**0**	**0.0**	**1**	**2.6**	
contra- and **ipsilateral above knee amputations and one extra ipsilateral amputation**	**0**	**0.0**	**1**	**2.6**	
Four amputations					
ipsilateral below-knee to above-knee and contralateral below-knee to above-knee amputations	***2***	***5.9***	***0***	***0.0***	
One amputation	61	64.2	77	67.0	0.677[2]
Two to four amputations	34	35.8	38	33.0	

[1]Chi-square test
[2]Fisher's exact test

Fifteen of Table 10's procedures may have been wound revisions (ipsilateral BK to BK or ipsilateral AK to AK). Ten patients had only one subsequent amputation at the same level as index amputation and all were ipsilateral AKAs. Twenty-two patients had ipsilateral transversions from BK to AK amputation; 22/210, (10%). Fifty patients ended up with a contralateral major LEA within two to four amputation operations; 50/210 (24%), and three had a bilateral major LEA at one session; that constituted of 53 patients with a bilateral major LEA, 53/210 (25%) during the follow-up period.

Thirty-five out of these 62 patients (removing those 10 patients with ipsilateral AK to AK) had diabetes mellitus (56%), four of them type-1 diabetes. Nine of the reamputated had prior toe amputations and two other amputees had transmetatarsal amputations, the latter of which were performed less than one month before the major LEA. Nine out of those eleven patients (82%) who had prior BK amputations had diabetes mellitus.

Reamputation was not an independent predictor of mortality among this series of 210 amputees.

5.3.5 Below knee/above knee -ratio

In 1998-2002, the below-knee vs. above-knee, i.e. BK/AK, ratio was 74/219=0.34. (The annual BK/AK ratios for the years 1998 to 2002 were 18/49=0.37, 13/46=0.28, 17/46=0.37, 15/39=0.38, and 11/39=0.28, respectively.)

5.3.6 Preventive revascularizations

PTA was performed on the same extremity as the index major LEA on a total of 49/210 (23%) cases and on 39/49 (80%) of cases less than six months before the major LEA. Respectively, the following surgical LERs were performed on 47/210 (22%) cases: Y prosthesis on 8/210 (4%) and 1/8 (13%) less than six months before the major LEA, bypass at the inguinal level on 29/210 (14%) and 14/29 (48%) less than six months before the major LEA, bypass at the suprapopliteal level on 18/210 (9%) and 13/18 (72%) less than six months before major LEA, and bypass at the infrapopliteal level on 4/210 (2%) and 4/4 (100%) less than six months before the major LEA. (Tables in Appendices 4 and 5)

Patients who had to stay at hospital for a prolonged time or who were discharged into long-term care or intermediate care had a significantly lower 1-year and an overall survival rate in both age- and gender-adjusted and multivariate analyses.

5.4. Study II

The mean age of the 119 amputees admitted from home for their index major LEA was 73.6 years (SD 11.5 years, 48% men). Fifty-one were able to return home and 68 were discharged into institutional care. Their background characteristics are shown in Table 7, divided by patients' discharge destination and prosthetic ambulation ability: discharged home with prosthesis, home without prosthesis, or into institutional care.

5.4.1 Predictors for institutional care discharge

Institutional discharge associated with sociodemographic variables were female gender, older age, and living alone in the univariate logistic regression model. Institutionalization was also associated with heart disease, unilateral AK or bilateral amputation, and not having diabetes combined with renal disease, or not having had a LER performed. The use of psycholeptics predicted discharge into institutional care, whereas use of serum lipid-reducing agents predicted discharge to home.

In the models adjusted for age and gender, those having unilateral AK or bilateral amputation, living alone, and using psycholeptics, had a higher risk of being discharged into institutional care.

Lastly, in the multivariate model, older age, living alone in preamputation, and unilateral AK or bilateral amputation at 31 days after the first major LEA were significantly associated with discharge destination into institutional care (Table 11).

5.4.2 Prosthesis usage among survivors

Of the 51 survivors returning home after their first major LEA, 36 (71%) received a prosthesis. The remaining 15 survivors had either: 1) a combination of age of 75 years or older and unilateral AK or bilateral amputation, or 2) a combination of unilateral AK or bilateral amputation and hemiplegia, paraplegia, uremia, or alcohol misuse.

Of the 68 patients who were discharged into institutional care, three (4%) had a prosthesis by one year, and 36 (53%) without prosthesis were 75 years or older and had a primary amputation level higher than below-knee. The remaining 29 patients were either younger than 75 years old (n=18) and/ or had below-knee as their primary amputation level (n=11). They did not receive a prosthesis, because 15 (52%) of them died within the first two to four months after primary major LEA and the remainder had comorbidities such as alcohol misuse, depression, dementia, hemiplegia, or cancer metastases.

In cross-tabulation, those amputees who received a prosthesis (n=39) were significantly younger ($p<0.001$), were more frequently men ($p=0.014$), lived with a companion ($p=0.006$), had unilateral BK rather than unilateral AK or bilateral amputation ($p<0.001$), and had diabetes ($p=0.013$) more frequently than those who remained non-ambulatory. Twenty-seven (51%) of the 53 patients younger than 75 and 12 (18%) out of the 66 of the 75-year-olds or older received a prosthesis.

Table 11 Predictors for being discharged into institutional care (n=68) among those PAD[1] patients admitted from home for first major LEA[2] and who lived more than 31 days after LEA (N=119). A logistic regression model.

Characteristic	Univariate analysis		Age and gender adjusted analysis		Multivariate analysis[3]	
	OR (95% CI)[4]	p-value	OR (95% CI)[2]	p-value	OR (95% CI)[2]	p-value
Gender						
Men	Ref.				Ref	
Women	2.50 (1.19–5.27)	0.016			1.50 (0.60–3.73)	0.388
Age						
<75	Ref.				Ref.	
≥75 years	4.40 (2.03-9.56)	<0.001			3.34 (1.41–7.95)	0.006
Companionship						
Lived with companion	Ref.		Ref.		Ref.	
Alone	3.67 (1.71–7.89)	<0.001	2.73 (1.17–6.38)	0.021	2.78 (1.11–6.99)	0.030
Amputation level 31 days after index LEA						
BKA[5]	Ref.		Ref.		Ref.	
AKA[6] and bilateral amputations	4.49 (1.96–10.30)	<0.001	3.56 (1.48–8.60)	0.005	3.66 (1.46–9.18)	0.006
Comorbidities (ICD10[7])[8]						
Cognitive impairment (F00-F03, or G30)	2.70 (0.99–7.40)	0.053	2.43 (0.83–7.18)	0.107		
or[9]	0.26 (0.08–0.79)	0.017	0.33 (0.10–1.11)	0.073		
Diabetes (E10-11) and renal disease (N04- N19) or[10]						
Heart disease (I11-I51, Z45, Z95)	2.20 (1.05–4.64)	0.038	1.92 (0.86–4.28)	0.109		
Previous revascularizations						
PTA[11,12] performed	Ref.		Ref.			
Not performed	2.28 (1.06-4.93)	0.036	2.27 (0.98-5.28)	0.056		
Surgical revascularization[9] performed	Ref.		Ref.			
Not performed	2.18 (1.03-4.59)	0.042	2.12 (0.94-4.80)	0.071		
Preamputation medication (ATC[13])[14]						
Analgesics (N02)	1.53 (0.73–3.20)	0.260	1.81 (0.80–4.08)	0.153		
Psycholeptics (N05)	2.21 (1.02-4.82)	0.045	2.66 (1.12-6.33)	0.027	2.23 (0.89–5.61)	0.088
Serum lipid-reducing agents (C10)	0.36 (0.15-0.92)	0.033	0.43 (0.16-1.15)	0.091		
Antihypertensives (C02, 3, 4, 7, 8, 9)	2.16 (0.89-5.22)	0.088	1.75 (0.67-4.57)	0.252		
Diuretics (C03)	2.00 (0.96-4.18)	0.065	1.23 (0.54-2.81)	0.624		

Certain analgesics (M01AB55, M01AC, M01AE and N02B)	2.09 (0.86–5.05)	0.104	1.77 (0.69-4.62)	0.232
Antibacterials for systemic use (J01)	0.50 (0.23–1.07)	0.075	0.58 (0.25-1.32)	0.191

[1]Peripheral arterial disease
[2]Lower extremity amputation
[3]Significant variables in age- and gender-adjusted analysis were included in multivariate analysis,
[4]Odds Ratio (95% Confidence Interval)
[5]unilateral below knee-amputation
[6]unilateral above-knee amputation
[7]International Classification of Diseases, 10th version
[8]Not having respective comorbidities used as a reference group
[9]MMSE<18, or when there were notes on suspicion of memory impairment, such as forgetfulness or poor memory in medical records, a patient was considered as having memory impairment. Mini-Mental-State-Examination (MMSE): 79 missing data
[10]Uremia in text
[11]Percutaneous transluminal angioplasty
[12]One or even several procedures of percutaneous transluminal angioplasty or surgical revascularization (Y prosthesis and other inguinal, suprapopliteal and infrapopliteal level surgical revascularizations) may have been performed on the same persons. A person was taken only once into analyses
[13]Anatomical Therapeutic Chemical classification system
[14]Not using respective medication is a reference group

5.2.1.1 Ambulation capacity according to classification from class I to class V

One year after primary major LEA, 13 (52%) out of 25 men and four (29%) out of 14 women using prostheses had reached useful ambulatory capacity, both outdoors and indoors, Classes I-III (Table 12). Of those prosthesis users able to return home, 16/36 (44%) were able to walk both in- and outdoors. One year later, 7 of class IV to V amputees had BK (32%), 13 AK (59%) and 2 bilateral amputations (9%).

Table 12 Numbers of patients with prostheses and their ambulatory capacity[1] by level of amputation and length of follow-up time

Amputation level	Follow-up time	Classes I-III n	(%)	Classes IV-V n	(%)	Total
BKA[2]	at one year	13	(65)	7	(35)	20
	at two years	11	(79)	3	(21)	14
	at end of follow-up	9	(82)	2	(18)	11
AKA[3]	at one year	3	(19)	13	(81)	16
	at two years	2	(15)	11	(85)	13
	at end of follow-up	2	(22)	7	(78)	9
BA[4]	at one year	1	(33)	2	(67)	3
	at two years	1	(25)	3	(75)	4
	at end of follow-up	0	(0)	2	(100)	2
Total	at one year	17	(44)	22	(56)	39
	at two years	14	(45)	17	(55)	31
	at end of follow-up	11	(50)	11	(50)	22

[1]by Narang et al., in 1984, as follows:
Class I=Ambulating with prosthesis and without any other walking aids indoors and outdoors
Class II=Ambulating with prosthesis indoors, but requiring one walking stick or crutch for outdoor activities
Class III=Ambulating with prosthesis and one crutch indoors, but requiring two crutches outdoors and occasionally a wheelchair
Class IV=Walking indoors with a prosthesis and two crutches or a walker, but requiring a wheelchair for outdoor activities
Class V=Walking indoors only short distances, mostly a wheelchair user
Class VI=Walking with aids, but without prosthesis
Class VII=Ambulates by wheelchair
Classes VI and VII not found in medical records.
[2]BKA=unilateral below-knee amputation; [3]AKA=unilateral above-knee amputation; [4]BA=bilateral amputation

5.5. Missing data while using patient records data (studies I and II)

Firstly, mobility before the interventions was insufficiently found in the patient records. Secondly, the missing data of smoking habits (39%) was common in the records of patients older than 65 years (n=181). From the data available the participants were classified as non-smokers, ex-smokers, and current smokers. The group younger than 65 years (n=29) included 14 non-smokers, 2 ex-smokers, and 12 smokers, and information about smoking habits was missing in one of their records only.

In study II, smoking habit data were missing on 21% (25/119).

Recordings of the evaluation of cognitive impairment were commonly missing, e.g., Mini-Mental State Examination (MMSE) was only found on 34% (40/119).

5.6. Study III

Since the first major LEA 2.7 years (range 1.0-7.0 yrs) and after the last major LEA 2.4 years (range 0.8-7.0 yrs) the interviewed amputees smoked or had smoked more than their age-and gender matched controls. The controls were more frequently married or lived with a companion, their place of residence was home, and their vocational status was significantly higher than that of the amputees. At the time of the interview amputees used cardiovascular secondary preventative medications and more psychopharmaceuticals than their controls. Twenty of the 25 amputees (80%) using prosthesis lived at home, 3 (12%) were in intermediate care and 2 (8%) in long-term care. Most of the prosthesis users had no cognitive impairment (17/23, 74%) assessed by the MMSE. (Table 13)

Table 13 Characteristics of the 59 amputees living either at home or in an institution at the time of interview

Characteristic	Home n (%) n=29	Institution n (%) n=30	p-value
Mean age at the time of interview in years	70.8 (SD[1] 11.9)	79.4 (SD[1] 7.3)	
Age at the time of the interview in years			**0.008**[2]
<65	7 (24)	1 (3)	
65-74	9 (31)	5 (17)	
75-84	12 (41)	16 (53)	
85+	1 (4)	8 (27)	
Gender			**0.027**[3]
Men	18 (64)	10 (36)	
Women	11 (35)	20 (65)	
MMSE[4]			**0.001**[2]
24-30[5]	18 (72)	7 (26)	
18-23[6]	6 (24)	8 (30)	
0-17[7]	1 (4)	12 (44)	
Level of amputation one year after their 1st LEA[8]			0.061[3]
BK[9]	9 (31)	4 (13)	
AK[10]	15 (52)	13 (43)	
BA[11]	5 (17)	13 (43)	
Had received prosthesis	20 (69)	5 (17)	**<0.001**[3]
Geriatric Depression Scale; 0-15			**0.007**[2]
≤4.9	21 (72)	8 (30)	
5-9.9	6 (21)	13 (48)	
≥10	2 (7)	6 (22)	
Psychopharmaceuticals			
Psycholeptics, N05	10 (29)	24 (71)	**<0.001**[2]
Sedatives, N05C	7 (26)	20 (74)	**0.001**[2]
Psychoanaleptics, N06	7 (24)	22(76)	**<0.001**[2]

[1]Standard deviation; [2]by Fisher's Exact Test; [3]by Chi-Square; [4]Mini-Mental-State Examination, where 7 were missed, of whom 4 had vision impairment and 1 end-state cancer, 1 left-side hemiparesis, 1 massive psychopathology; [5]no cognitive impairment, [6]mild cognitive impairment, [7]severe cognitive impairment; [8]lower extremity amputation; [9]below-knee, [10]above-knee, [11]bilateral amputation

5.6.1 Health-related quality of life and functional well-being

The amputees had a lower health-related QoL assessed with 15D HRQoL (Figure 9) and with the Rand-36 PF than their age- and gender-matched controls (Tables 14 and 15). The 15D HRQoL with home-dwelling amputees was similar to their controls (p=0.457), but their QoL with Rand-36 PF was lower (p<0.001) than their age- and gender-matched controls.

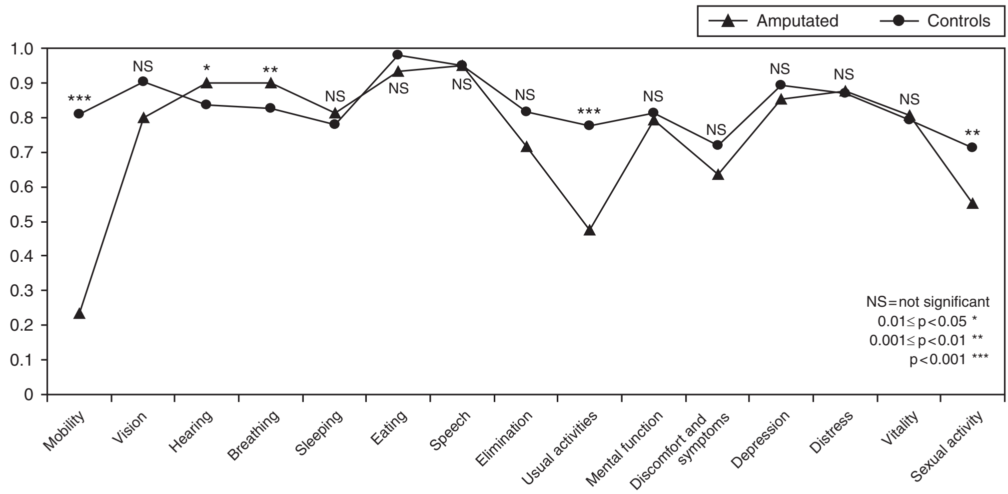

Figure 9. The 15D Health-related quality of life profile

5.4.1.1. Depressive symptoms

The GDS profile shows amputees feeling more helpless, worthless, that their situation is hopeless, and that 'most people are better off' when compared to their controls (Figure 10).

The amputees had significantly more depressive symptoms than their controls; 48% versus 32%. After adjustment for age, the institutionalized amputees (mean 6.08, SD 3.74) had depressive symptoms more regularly (p=0.013) than home-dwelling amputees (mean 3.55, SD 2.80).

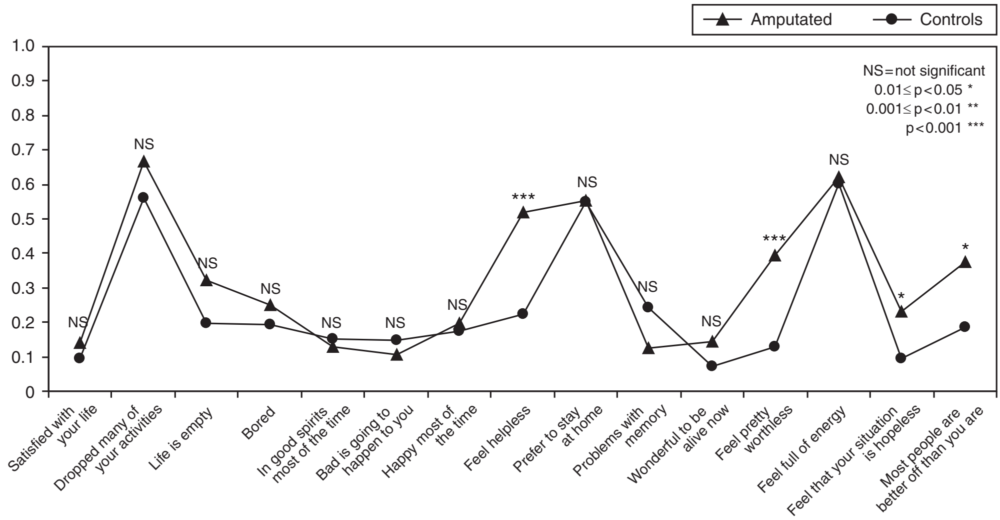

Figure 10. The Geriatric Depression Scale profile, study III

5.4.1.2. Perceived state of health

The amputees were pleased with their state of health, but not significantly more in Rand-36 GH than their controls (Tables 14 and 15).

Table 14 Mean scores of quality of life (QoL) scales of the amputees according to their place of residence, in an age-adjusted analysis only, and then between the amputees and their age- and gender-matched controls analyzed with a linear mixed model with stratum as a random effect

Scale	Amputees according to their place of residence N=59		p-value[1]	All amputees together N=59	Controls N=118	p-value[2]
	Home, n=29	Institution, n=30				
	Mean (SD[3])	Mean (SD[3])		Mean (SD[3])	Mean (SD[3])	
15D HRQoL[4]	0.82 (0.1)	0.67 (0.1)	**0.001**	0.74 (0.1)	0.83 (0.1)	**<0.001**
RAND-36 PF[5]	22.64 (24.3)	2.93 (10.3)	**0.014**	12.8 (21.0)	60.5 (29.7)	**<0.001**
SSQ6N[6]	2.19 (1.5)	1.06 (0.6)	**0.002**[7]	1.65 (1.3)	1.3 (0.7)	0.071[7]
GDS[8]	3.55 (2.8)	6.08 (3.7)	**0.013**[9]	4.8 (3.5)	3.7 (3.2)	0.071[9]
LS[10]	8.52 (2.9)	10.36 (4.1)	0.098[9]	9.4 (3.6)	8.9 (3.4)	0.448[9]
RAND-36 GH[11]	58.62 (18.7)	53.51 (24.6)	0.180	56.1 (21.7)	54.0 (19.1)	0.539

[1]Age adjusted model; number of missing values were 1-4 in institution group
[2]Linear mixed model with stratum as a random effect; number of stratums varied between 56 and 58
[3]Standard deviation
[4]15D Health-related Quality of Life Instrument; range: 0-1; a higher value means better QoL; (Sintonen, 2001)
[5]RAND-36 *Physical Functioning* subscale; range: 0-100; Q 3-12; a higher value means better QoL; (Hays et al., 1993);
[6]Sarason's 6-item Social Support Questionnaire Number Score; range: 0-36; a higher value means better QoL; (Sarason, 1987)
[7]Values were square root transformed for statistical analyses
[8]Geriatric Depression Scale; range: 0-15; a lower value means better QoL; (Lyness et al., 1997; Yesavage et al., 1982)
[9]Values were logarithmically transformed for statistical analyses
[10]Life Satisfaction Score; range: 4-20; a lower value means better QoL; (Koivumaa-Honkanen et al., 2000)
[11]RAND-36 *General Health*; range: 0-100; Q 1,33-36; a higher value means better QoL; (Hays et al., 1993)

Table 15 Distributions in different quality of life scales with amputees and their age and gender matched controls

Scale	Amputees, N=59 n (%)	Controls, N=118 n (%)	p-value[1]	OR[2] (95% CI[3])
2 Items from Rand-36 PF[4]				
Climbing one flight of stairs				
No limitations	5 (9)	67 (60)		
Some limitations or a lot of limitations	53 (91)	45 (40)	**<0.001**	15.78 (6.20-40.17)
Walking about one hundred meters				
No limitations	4 (7)	83 (74)		
Some limitations or a lot of limitations	54 (93)	29 (26)	**<0.001**	38.64 (13.98-106.82)
Perceived social support				
From spouse or a companion	22 (40)	55 (53)	0.097	0.59 (0.32-1.10)
From other near relatives	47 (85)	66 (63)	**0.004**	3.38 (1.46-7.82)
From a close friend	25 (45)	36 (35)	0.162	1.57 (0.83-2.97)
From a close work mate	15 (27)	3 (3)	**<0.001**	12.63 (3.07-51.88)
From a close neighbor	15 (27)	11 (11)	**0.010**	3.17 (1.31-7.66)
From another close person	22 (36)	9 (9)	**<0.001**	6.03 (2.66-13.68)
From no one[5]	23 (42)	11 (11)	**<0.001**	6.08 (2.68-13.80)
Geriatric Depression Scale; 0-15				
≤4.9	29 (52)	73 (68)		
5.0-9.9	19 (34)	27 (25)		
≥10.0	8 (14)	7 (7)	**0.038**	2.05[6] (1.04-4.05)
Self-reported Life Satisfaction score				
Satisfied (4-6)	12 (21)	25 (22)		
Intermediate group (7-11)	32 (56)	62 (56)		
Dissatisfied (12-20)	13 (23)	25 (22)	0.870	1.05[5] (0.57-1.93)
Perceived state of health				
Good (1-2)	24 (42)	48 (43)		
Moderate (3)	22 (39)	49 (43)		
Poor (4-5)	11 (19)	16 (14)	0.696	1.12[5] (0.62-2.03)

[1]Logistic regression using generalized estimating equations
[2]Odds ratio expresses the strength of the connection; >1 means that amputees have more and <1 that controls have more of the characteristic in question
[3]Confidence interval
[4]Rand-36 *Physical Functioning* subscale;
[5]Lacking social support in at least one of the six items of the 6-item Social Support Questionnaire
[6]Cumulative odds ratio

5.4.1.3 Life satisfaction and perceived social support

The amputees had similar life satisfaction than their controls. The amputees found themselves satisfied and felt contented, whether or not they lived in long-term care or at home (Table 14 and 15).

There was a concomitant tendency of dissatisfaction, more depressive symptoms and lack of social support in at least one of the six items of the SSQ6N more commonly among the amputees than among their controls. On the other hand, many amputees also felt they received more support from close relatives, their neighbors, and other close persons, or from an old workmate than their controls (Table 15).

All QoL scores of the amputees had a significant correlation with the SSQ6N score, but among the controls only Rand-36 PF correlated significantly with the SSQ6N score. Among the amputees, all QoL scores correlated significantly with the LS score, but among the controls SSQ6N did not correlate significantly with the LS score, but the other correlations were significant.

5.7. Study IV

5.7.1 Quality of life

Patients showed more depressive symptoms than their controls, and according to LS scores they were more dissatisfied than their controls (Table 16). In general, PAD patients who had undergone revascularizations showed lower QoL than their age- and gender-matched controls. The 15D HRQoL profile shows the general view of the difference in QoL between them (Figure 11). Secondly, there were no significant differences between the QoL of those who had undergone endovascular and/or surgical revascularization. Patients had poor physical functioning according to RAND-36 PF. Less than one half could walk 100 meters without difficulty, and only a quarter could manage 500 meters without difficulty. Patients got more support from a close person outside of the family such as a home nurse or other caring professional. On the other hand, they more commonly perceived that they did not get support from anyone. In comparison, the controls received more support from their spouse or companion than the patients. (Table 16)

Table 16 Distributions in different quality of life (QoL) scales with PAD patients and their age- and gender-matched controls

QoL variables		**PAD patients N=231** n (%)	**Controls N=231** n (%)	**p-value**[1,4]	**COR**[2, 4] **(95% CI**[3,4]**)**
Social support from; n=224					
	Spouse or a companion[6]	115 (51)	161 (72)	**<0.001**	0.41[5] (0.29-0.59)
	Other near relatives[6]	138 (62)	121 (54)	0.100	1.37[5] (0.94-1.98)
	A close friend[6]	80 (36)	88 (39)	0.450	0.86[5] (0.58-1.27)
	A close workmate[6]	9 (4)	13 (6)	0.373	0.68[5] (0.29-1.59)
	A close neighbor[6]	22 (10)	22 (10)	1.000	1.00[5] (0.53-1.90)
	Another close person[6]	37 (17)	16 (7)	**0.003**	2.57[5] (1.39-4.75)
	'No one'[7]	43 (19)	20 (9)	**0.002**	2.42[5] (1.38-4.27)
Rand-36 PF[8]					
Ability to walk					
Walking about 2000 meters; n=220					
	No limitations	21 (10)	123 (56)		
	Some limitations	64 (29)	58 (26)		
	A lot of limitations	135 (61)	39 (18)	**<0.001**	6.39 (4.43-9.21)
Walking about 500 meters; n=222					
	No limitations	63 (28)	160 (72)		
	Some limitations	73 (33)	41 (18)		
	A lot of limitations	86 (39)	21 (10)	**<0.001**	5.70 (3.78-8.60)
Walking about 100 meters; n=225					
	No limitations	106 (47)	187 (83)		
	Some limitations	74 (33)	31 (14)		
	A lot of limitations	45 (20)	7 (3)	**<0.001**	3.31 (2.14-5.12)
GDS[9]; n=219					
	≤4.9	103 (47)	171 (78)		
	5.0-9.9	65 (30)	39 (18)		
	≥10.0	51 (23)	9 (15)	**<0.001**	4.31 (2.88-6.44)
LS[10]; n=231					
	4-6	17 (7)	71 (31)		
	7-11	119 (52)	131 (57)		
	12-20	95 (41)	29 (12)	**<0.001**	5.14 (3.46-7.63)
Perceived state of health; n=229					
	Good (1-2)	50 (22)	146 (64)		
	Moderate (3)	109 (48)	70 (30)		
	Poor (4-5)	70 (30)	13 (6)	**<0.001**	6.52 (4.48-9.51)

[1]<0.05 is considered significant
[2]Cumulative odds ratio, >1 means worse quality of life in PAD patients compared to controls
[3]Confidence interval
[4]Logistic regression using generalized estimating equations to account for age- and gender matching
[5]Odds ratio
[6]Getting social support in at least one of the six items of the 6-item Social Support Questionnaire; (Sarason, 1987)
[7]Lacking social support in at least one of the six items of the 6-item Social Support Questionnaire
[8]Rand-36 *Physical Functioning* subscale; Q 3-12; (Hays, Sherbourne, & Mazel, 1993)
[9]Geriatric Depression Scale, range: 0-15; a lower value means better QoL; (Yesavage et al., 1982)
[10]Life Satisfaction score, range 4-20; the lower value means better QoL; (Allardt, 1973).

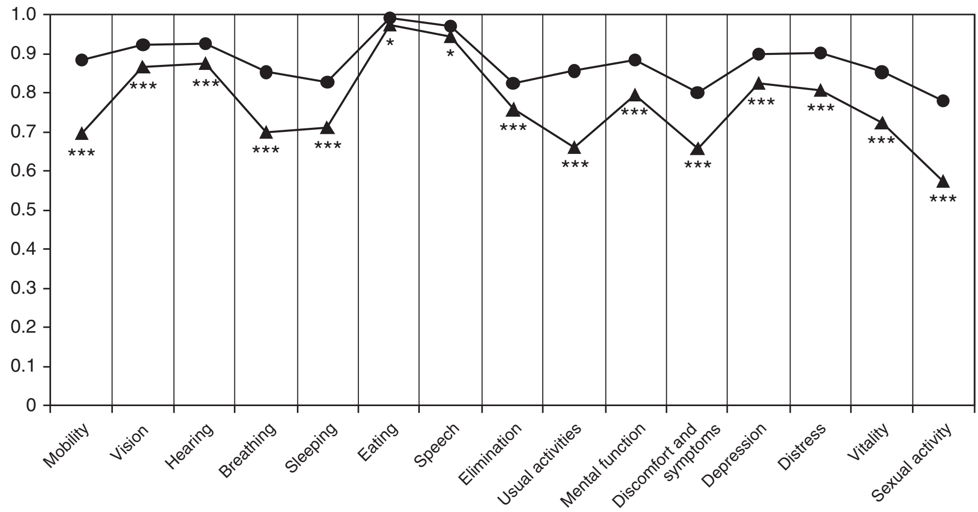

Figure 11. 15D HRQoL profile for the PAD patients and their age- and gender-matched controls.
-▲-PAD patients after endovascular procedures -●- controls
NS=not significant, $0.01 \leq p<0.05$ *, $0.001 \leq p<0.01$ **, $p<0.001$ ***.

There was clear co-linearity between all QoL measures. Low 15D HRQoL, Rand-36 PF, and high GDS, and LS predicted a low 'perceived state of health' in both the patient and the control groups ($p<0.001$). Similarly the inability to walk was associated with a poor 'perceived state of health' amongst patients ($p<0.001$). The same association tended to be similar among the controls ($p=0.047$). Those patients who felt they were given more social support were associated with having a better 'perceived state of health' compared to those individuals who did not feel they were given support. The latter association did not exist among the controls.

6. DISCUSSION

The aim of the study originated from a sad thought, which occurred several years ago: why are the people attending the prosthetic rehabilitation group in such poor shape? In this study incidence, mortality, and subjective health status together with QoL measurements of people who have undergone a major LEA due to PAD –the most common reason for LEAs– have been evaluated. In addition, the subjective health status of patients with severe PAD and achievement of limb salvage through LERs has been analyzed, and is now discussed.

6.1. External and internal validity of the study

6.1.1 Strengths of the study

The data in studies I, II and III included all amputees of the study period and area.

As well, the strength of the Study IV was that original patient populations covered all PAD patients with revascularizations during the given period and from the specified district. One and the same researcher carefully examined all medical records twice.

The case-control study design in Studies III and IV ensured the QoL outcome was comparable between cases and their controls sharing the same age, community and historical period of life.

A high number of responses were reached in both of these studies, so that almost all QoL assessments case-control pairs could be analyzed making the results reliable. All measures of perceived status of health and QoL used were reliable and widely used in research purposes. Furthermore, all of them had Finnish versions.

6.1.2 Study limitations

The series of the amputees was small, comprising only 210 patients. Studies I and II being retrospective medical record reviews, some important information concerning the prognostic factors among the amputees was often lacking. Data, especially from the rehabilitation point of view, such as preamputation ambulatory capacity, global physical functional capacity or evaluation of cognitive function (including also an up-to-date MMSE) were often missing.

From the research point of view, it is unfortunate that psychological and cognitive functional tests were not found to be carried out. But since decisions are mainly made according to knowledge recorded in medical notes, this means that, in clinical practice, the value of psychological and cognitive capacity is not fully understood for maintaining mobility after amputation.

One very important predisposing factor, smoking (Wattanakit et al., 2005), was also found to be poorly recorded in the medical records. For some reason, doctors had not regularly recorded these old patients' smoking habits. Therefore, it was not possible to include the important PAD risk factor of smoking habits in the statistical modeling.

The degree of renal insufficiency was difficult to assess from the records. Variables indicative of the severity of diabetes should also be recorded in detail. Perhaps there was more concern over diabetic neuropathic changes than purely vascular changes in peripheral arteries.

For practical reasons, age and gender, and not the place of residence were used for matching criteria in the Study III. That led to a situation where most controls lived in their own homes, while half of the amputees lived in institutions. Most individuals in long-term care move less than they would move at home. They also have more comorbidities and medication.

The fact that the amputees were personally interviewed and the controls completed postal questionnaires only, may have influenced our results, e.g. in the amount of social support reported by the controls. Comparison of the morbidity data may suffer from self-administered answers of the controls in the postal questionnaires. For the comorbidity data it would have therefore been better, had it been possible to carry out a medical data review. However, the same structured questionnaire was used for both cases and controls, although the MMSE was performed for the amputees only during the interview.

Different interviewers, e.g., nurses or lay persons and respondents in postal inquiries may give varying information on diagnoses and medication (Brogger et al., 2002). Neither inter-rater reliability nor test-retest reliability was tested for the questionnaire. The patients were only expected to give answers to the clear-cut questions of the QoL scales, and thus the responses of the scale items were relied on.

6.1.3 Representativeness of the study samples

In Study I, the amputation incidence rates were standardized for age and gender, using the December 31, 2005 population of Finland as reference. Therefore, the standardized incidence rates in this study may be compared to the overall amputation rates in Finland or some other district or city with a population composition similar to that in Finland.

Study II was a pure medical record review describing the predictors for institutionalization, which type of accommodation is a burden to both community and individual, and also the ambulatory capacity of the patients and ambulatory capacity predictors.

Study III particularly in relation with rehabilitation sphere of patients' post major amputation period: The practical issue this study brings out is to become aware of how ill people who are bound to lose their leg due to PAD are. In fact, many of them die soon after their amputation due to reasons other than their leg; quite often their heart cannot bear the stress [very high post-operative (within 30 days) mortality and high at 12 month mortality rate]. If they survive, these patients might be so exhausted that they cannot stand the amount of rehabilitation and training that would otherwise be necessary to avoid extra muscle weakening due to along period of being bed-bound.

Study III had about 30 % of the original amputated patient population, and Study IV patients covered 80% of the survivors after revascularization. The results of the studies may only be generalized to survival cohorts among PAD patients after LER (IV) or LEA (III) (Fletcher, 2005) Since the follow-up time varied 0.3-6.4 years from the time of intervention, in Study IV, the fact that recurrence of symptoms may occur at different time points, might have also affected the QoL.

6.1.4 Importance of measuring the quality of life and the perceived functional status of patients

QoL measurements give all members of the treatment chain a better understanding of the patient's subjective state of health: even a generic instrument gives it if several scales measuring different domains of QoL are used together. These may offer a good way to follow the rehabilitation process. If the QoL was measured at the beginning of the training period for prosthesis use, and then subsequently checked throughout the follow-up period, the improvement of QoL by Rand-36 would also be very promising for the amputee.

Participants' perceived status of health and QoL was measured multidimensionally, by triangulating to understand the aspects of their health-related quality of life. Triangulation is expected to strengthen the basis for conclusions to be drawn from the study and add its reliability (Cohen, 2002; Last, 2001). The QoL was approached by viewing it through the domains of physical functioning, mental state and socio-psychological attitudes or behavioral attitudes towards life in general. Positive correlations between all other QoL scores used and the social support score and separately between the life satisfaction score of the amputees, indicate that the scales used focused on the same issue. As well the fact that there was clear co-linearity between all QoL measures as to the 'perceived state of health' of the PAD patients and their controls were concerned refers to the same thing.

6.2. Consideration of the findings

6.2.1 Participants

Amputated as well revascularized patients seemed to constitute samples of severely ill patients. The mean age of the amputated patients was high, as elsewhere in Finland (Eskelinen et al., 2001; Pohjolainen and Alaranta, 1999) and in industrialized countries in general (Wong, 2006). The revascularized patients were somewhat younger than the amputees, and the surgically revascularized were younger than endovascularized, which is in line with expectations (Eskelinen et al., 2001).

6.2.2 The incidence rates of amputations

The incidence rates of amputations in the city of Turku were considerably high compared to some other reports from elsewhere (Melillo et al., 2004; Pohjolainen and Alaranta, 1999; Sandnes et al., 2004). However, comparison of incidence rates is difficult even in Finland, because some Finnish studies rely exclusively on the national registers maintained by THL, Finland. They register all operations and their codes, and index amputations cannot be differentiated from the overall records. Some studies, such as ours, have overviewed all medical records of the amputees in their study area. Some have not used a reference population in their calculations.

Sandnes and co-workers reported their standardized amputation rates from the State of Washington. They had also included toe and metatarsal amputations. The incidence rates were 22.3-30.6/100 000 person-years. However, minor amputations accounted for approximately one third of all LEAs (Sandnes et al., 2004). The incidence rates of AK and BK amputations in Turku ranged from 27.1 to 19.5/100 000 person-years, showing a slight decrease over time. Furthermore, our rates did not include traumatic or reamputations, as do many other reports (Carmona et al., 2005). LEA incidence rates are decreasing (Winell et al., 2006). However, the number of the amputees will stay relatively large. Ziegler-Graham et al (2008) have predicted that due to the fact that in the year 2005 there were 1.6 million persons living with the loss of a limb in the USA (38% of them had an amputation secondary to dysvascular disease with a comorbid diagnosis of diabetes mellitus), the number of US citizens living with the loss of a limb will more than double by the year 2050 to 3.6 million. If incidence rates secondary to dysvascular disease can be reduced by 10%, this number would be lowered by 225 000. (Ziegler-Graham et al., 2008)

6.2.3 Mortality and its predicting factors

The standardized mortality ratio after the first year following the index amputation in the study group is comparable to the earlier studies. Ebskov and co-workers reported SMR figures from 8.4 to 8.9 (Ebskov, 1999).

The presence of cardiovascular disease predicted both early and late postoperative mortality. The patients who died within one month most likely had a severe cardiovascular disease, and their gangrenous leg was amputated as mere pain relief for their final days.

Therefore, individual perioperative assessment should be carried out according to defined criteria. For example, the Eagle criteria include age >70 years, angina, diabetes, Q wave on ECG, and history of congestive heart failure (Back et al., 2003; de Virgilio et al., 1996; Matsuura et al., 1997). The cardiac medication should be adjusted perioperatively (Schouten et al.).

The survival of AK amputated patients is known to be shorter than that of patients with BK amputations (Aulivola et al., 2004; Pohjolainen and Alaranta, 1998). Among patients in this study, unilateral AK amputations predicted the overall mortality in univariate analysis only. On the other hand, 79% of the BK amputated patients were younger than 65 years.

LERs had probably been done electively to the patients who were expected to have a higher survival rate. In fact, their early survival was better than that of the ones who had not had surgical reconstruction, but the later mortality figures were similar to those of the other patients. (Zeller et al., 2009; Rowe et al., 2009)

6.2.4 Reamputations

During the four to eight year follow-up, the ipsilateral, from BK to AK reamputation rate was 10%, which is in accordance with Izumi and his co-workers who report on true reamputation of first-time amputation with a seven to ten year follow-up of diabetic patients, being 13.3% at five years. Their contralateral major LEA reamputation rate was 53.3% at five years, while in this study it was 24% during our follow-up. (Izumi et al., 2006)

A reamputation is a serious and stressful procedure for the patient. Even a wound revision is a sign of prolongation of the convalescence after LEA which delays the possible prosthetic rehabilitation. The condition of the contralateral lower extremity is essential to determine during the perioperative time.

6.2.5 Institutionalization after major lower extremity amputation

In Finland, there is a general opinion or belief that elderly Finns have been in institutional care more frequently than other elderly Europeans. There is an active policy to change this situation. The present patients, however, were so frail that many of the ones who were admitted from home died during the early follow-up, and survival was even shorter if their condition did not allow them to return home any more.

Positively inspiring social activities and physical training groups for the elderly should be organized already before any amputation. However, physical rehabilitation and psychological help following amputation are fundamental.

In this study, the main predictors for institutionalization were older age, living alone, and more invasive amputation (AK or BA). Depression and dementia are one of the most common causes of dependency and being forced to move into institutional care in old age (Anstey et al., 2007). However, loss in mobility also causes dependency. Disability usually occurs first in mobility, and mobility difficulty predicts the onset of disability in tasks essential to living independently in the community (e.g. shopping, meal preparation) and caring for oneself (e.g. bathing, dressing). (Harris et al., 1989) At least half of end-stage disability in self-care tasks results from such a progressive decline in function, whereas the remaining half may occur catastrophically due to a medical event, e.g. stroke (Ferrucci et al., 1996) or CLI and amputation.

Most of the patients who received a prosthesis were able to return home. Those who had a distinct comorbid condition, e.g. hemiplegia, dementia, or an extra burden of alcohol misuse became non-ambulatory.

6.2.6 Prosthesis usage

Although the mortality of the series was very high, the prosthesis use of the surviving patients' was in accordance with other reports (Nehler et al., 2003a). Of those who returned home and survived more than one year after primary amputation, two-thirds of the patients had received a prosthesis, and just under half of the prosthesis users were able to walk both in- and outdoors. Prosthesis use was related to younger age, type of amputation, and better health. Compared to an earlier Finnish follow-up from Southern Finland (Pohjolainen et al., 1989), where 27% of 267 PAD patients and 25% of the 245 diabetics 25% died within two months, and evidently after that 55 PAD patients and 74 diabetics were fitted with a prosthesis, our results might resemble those figures from this earlier decade. In 2005, Geertzen and his co-workers observed that the chances of walking 500 m or more decrease with an increase in age and a more proximal amputation (Geertzen et al., 2005). They estimate the ability to walk 500 m or more enabled adequate activities of daily living (ADL) independence and is a positive determinant with respect to quality of life in amputees. In the grading system of Narang and his co-workers (Narang et al., 1984), walking distance is not evaluated together with ambulatory capacity. In 2005, Taylor and his co-workers stated that younger healthy patients with BK amputations achieved functional outcomes similar to what might be expected after successful lower extremity revascularization (Taylor et al., 2005a). They suggest that amputation in these instances should probably not be considered failed therapy, but another treatment option that is capable of extending functionality and independent living. The knee joint enables good bipedal gait with contemporary prostheses (Nehler et al., 2003a).

Amputation should not be considered as an end-of-life event, but rather as a realistic form of care if performed at the proper moment, so that long bed rest with long-healing ulcers does not diminish the functional capacity of a patient with already weakened musculature and balance.

6.2.6.1 Prosthesis versus wheelchair use

Only 33% gained prosthetic ambulation capacity and most of the amputees were either institutionalized or lived as non-ambulatory in their homes. In our medical records, class VII expressing wheelchair use was not found, although it would be beneficial and important to be able to independently use a wheelchair.

Both prostheses and wheelchairs have become lighter during the past few decades.

According to Chin and his co-workers, a lower amount of comorbidity, good ability to stand on the remaining leg, and a strong will to walk were found to be important factors contributing to successful prosthetic rehabilitation. Age alone is not an important factor. (Chin et al., 2002) However, training walking after a long interval of decreased mobility with chronic critical ischemia is a remarkable stress for the cardiovascular system of an amputee. Oxygen uptake with a proximal prosthesis is higher than with a distal one, and so walking with an AK prosthesis is more demanding for the heart than a BK prosthesis. Coronary artery disease or cardiac insufficiency, naturally reduce the oxygen uptake necessary for strenuous exercise such as walking with a prosthesis for, e.g., a transfemoral stump. (Chin et al., 2002)

Cardiorespiratory capacity determines postamputation capability to move, and to maintain one's preamputation independency in the community. Cerebrovascular diseases, e.g. hemiparesis diminish prosthetic ambulation possibilities. Moreover, cognitive impairment and dementia may hinder prosthesis use. Therefore, it would be desirable not only to have physical fitness evaluated early enough at the preamputation stage and after amputation, but also MMSE for evaluating cognitive capacity. If a patient is not using prosthesis, learning wheelchair use and transfer activities may also be an important rehabilitation target for e.g. those who are partially dependent but living in a home like-dwelling. Nevertheless, proper regard for wheelchair ambulation might be good to take into consideration when inevitable amputation is planned and the possibility to use a wheelchair cannot be understated (Houghton et al., 1992), for a person who is of high age and might not be able to go through the heavy rehabilitation process needed for good prosthesis ambulation.

On the other hand, mobility in institutional care is not always supported by active physiotherapy as the general health status of an amputee does not always allow much active wheelchair use practice. In this way, loss of independency might further increase (Gillis and MacDonald, 2005; Hoenig and Rubenstein, 1991).

6.2.7 Quality of life outcome

6.2.7.1 Perceived physical functioning after amputation

PAD amputees, who had survived approximately for three years after their first major lower extremity amputation, reported to have similar life satisfaction, social support network and general state of health as their age- and gender-matched controls. The physical functioning of the amputees was notably worse than their age- and gender-matched controls, as also Pell and his co-workers reported, in 1993. They note that amputees had more problems with mobility, social isolation, lethargy, pain, sleep and emotional disturbance than controls; the 'mobility' variable remained as an independent factor in their multivariate logistic regression analyses. The 'social isolation' and 'emotional distress' variables lost their significance after adjustment for mobility, so they suggest that much of the poor quality of life is secondary to restricted mobility. Therefore, rehabilitation following amputation should focus on attempts to improve mobility. Most individuals in long-term care move less than they would move at home; they have poor mobility. The great majority of the patients had either AK or bilateral amputation. Hence, greater instruction in the use of wheelchairs should be included into our rehabilitation programs in order to improve mobility and social integration. (Pell et al., 1993)

6.2.7.2 Social support /importance of social network

Amputees who lived at home had a larger social support network and more available social support than their controls, whereas social isolation was found in those who lived in institutional care. Those individuals who have no-one to support them should be identified.

The ability to feel that one was getting support was also important for the revascularized patients. When under stressful situations, however, many of them did not feel that this support was given.

It would be valuable to evaluate perceived social support and the size of social network already during the perioperative period, in order to focus on this aspect during rehabilitation and for the hospital discharge plan (Deans et al., 2008). Likewise, a social support survey would help the staff organize peer and support persons to visit long-term care patients and home-dwelling amputees.

> Rehabilitation planning necessitates that a proper comprehensive assessment is carried out for the patient. In doing so, depression must be taken into account, not only by medicating for it, but also by introducing fresh, innovative, and active sports programs to give both mental and social peer support.

Steinbach has reported that social networks diminish the likelihood of institutionalization and mortality (Steinbach, 1992). Old people who participated in some form of social activity were also found to have a risk of institutionalization of almost one-half, whereas living alone increased the likelihood of institutionalization. Participating in social activities and visiting or talking with friends or relatives were negatively related to the likelihood of mortality (Steinbach, 1992). In the medical record studies I and II social networks were not found to be reported, even though the existence of social networks may be essential for the on-going rehabilitation process. It is easier to cope with changed circumstances in mobility and health if there are informal caregivers, a partner or other friendship relationships (Gooberman-Hill and Ebrahim, 2006). Patients who live alone after hospitalization are less likely to improve in ADL function, and are more likely to be admitted to a nursing home in the subsequent month. Such patients may benefit from increased social and medical support to maintain independent living and improve function (Mahoney et al., 2000). In an optimal situation, social factors should be assessed at the time revascularizations are planned for PAD patients.

6.2.7.3 Cognitive ability

Cognitive ability also crucially affects amputated patients QoL, e.g. putting on the prosthesis becomes almost impossible without help from another person (Rafnsson et al., 2009). In this study, the helplessness of the amputees, seen in the GDS profile, was obvious; e.g. not being able to put on a prosthesis or difficulties in using a wheelchair may cause frustration and anger.

6.2.7.4 Depression and anxiety

Depression and anxiety are common up to two years post-amputation, and appear to decline thereafter to general population norms (Horgan and MacLachlan, 2004). In this study, the difference was still found three years after the amputation, but emphasized that those who lived in institutional care had the worst QoL and the highest level of depressive symptoms. The institutionalized amputees were commonly medicated with psycho-pharmaceuticals, but e.g. a depression diagnosis was seldom reported by the participants, nor was it found in the medical records. On one hand, dementia and depression are common diagnoses of old people in long-term care today (O'Hara et al., 2002), as well as being common with the institutionalized amputees in our study. On the other hand, GDS and other verbal depression scales do not give reliable results as far as patients with low cognitive abilities are concerned (Debruyne et al., 2009).

The relationship between life dissatisfaction, increased mortality and adverse health behaviour might support the use of LS scales as a cumulative health risk indicator (Koivumaa-Honkanen et al., 2000). An optimistic personality disposition and active attempts at coping return when enough time has passed since amputation (Horgan and MacLachlan, 2004).

GDS indicated depressive symptoms among patients. Unlike their controls both amputees and revascularized patients also used more psychopharmaceuticals. There might have been clinical signs of depression, but proper evaluation of this disease has evidently not been carried out for all who needed it. Clinical depression, as it is, should be diagnosed in two stages: an effective approach could be that doctors would routinely use screening scales, such as those with well-defined cut-off points, which GPs or psychiatrists could use to make a proper clinical evaluation of the depression of patients. Depressed PAD patients have been found to have a worse outcome in their revascularized leg (Cherr et al., 2007). Moreover, many patients continued smoking irrespective of their life threatening disease, and by smoking they might have masked depressive symptoms from themselves (Breslau et al., 1998; Khaled et al., 2009).

’Type-D personality’ is defined as having a tendency to experience negative emotions and being socially inhibited. Aquarius and her co-workers have found it predicting PAD patients’ poor physical health and decreased level of independence as well as depressive symptoms in patients with PAD above and beyond ABI. Additionally, they found it predicting poor overall QoL, controlled for age, gender, PAD severity, and cardiovascular risk factors. In the current study, both among amputees and revascularized patients, there were some individuals who had abundant depressive symptoms, were dissatisfied and had no perceived social support in some of the six items of the SSQ6N. This might indicate a type-D personality. Because of this, it is important to account for personality when evaluating patient-based outcomes in the context of PAD. (Aquarius et al., 2007)

Feelings of ‘perceived control’ are crucial for maintaining functional ability in later life (Kempen et al., 1999b). It is reasonable to assume that effective care of depressive symptoms enhances the perceived physical functioning and *vice versa*. Preventing an increase in depressive symptoms may further help prevent deterioration in physical functioning in poorly functioning older persons (Kempen et al., 1999a). Hence, an assessment of depression in elderly adults is crucial, because depression diminishes QoL, increases mortality, and causes extra health care costs (Loughlin, 2004).

Proper management of pain and medical comorbidity may mitigate depressive symptoms anyway, as well as discussion about depressive symptoms and their treatment options (Darnall et al., 2005).

However, it is possible that some of the amputees, both older and younger individuals who had many difficulties in daily living, are such personality types whose ability to be satisfied with life has kept them alive. They may have a problem-solving, salutogenic capability (Lindstrom and Eriksson, 2006). Whatever the case, it is reasonable to assume that good LS and salutogenic capability create a prerequisite for a health promoting trajectory. Personal coping mechanisms might be worth exploring among these seriously ill arteriosclerotic patients (Desmond and MacLachlan, 2006).

In order to make invasive endovascular or surgical LERs more effective, it is necessary to concentrate on these patients' rehabilitation and exercise programs. The poor results in mobility and overall physical functioning call for exercise rehabilitation planned specifically for PAD patients.

Major LEA incidence rate is most likely decreasing (Egorova et al.; Eskelinen et al., 2004; Winell et al., 2006), but the long-term perceived functional capacity of patients after LER remains poor. The incidence rate of major LEAs might be decreasing because of 1) LERs: endovascular, surgical, or hybrid operations, where endovascular and surgical revascularizations are performed during the same session, or 2) endovascular procedures are performed using better devices, or 3) the general level of education and health awareness has been raised and thus people a) seek care earlier, b) make life-style modifications and c) have better medication, e.g. statins. However, a major LEA should not be considered an end-of-life event. The technical quality of prostheses has improved remarkably compared to the techniques that were available a few decades ago, broadening the possibilities of successful prosthesis ambulation.

7. CONCLUSIONS

The following major findings and conclusions were made:

1. The incidence rates of major low extremity amputations (LEA) in the City of Turku were considerably high in 1998-2002, however the annual incidence rates decreased from 1998 to 2002. Reamputations were common during the 4 to 8 years of follow-up. Mortality during the first year after major LEA was high then levelled out to almost the same as their coevals. Cardiovascular diseases predicted high mortality after LEA. (Study I)
2. The majority of amputated patients could not return home after their first major LEA. Older age, living alone before the amputation, and unilateral above-knee or bilateral amputation at 31 days after the first major LEA were significantly associated with discharge destination into institutional care. Most elderly amputees remained non-ambulatory. (Study II)
3. Home-dwelling amputees had a relatively good life satisfaction and perceived state of health even when compared to their age- and gender match controls whereas amputees living in long-term care had a lot of depressive symptoms (Study III).
4. By using triangulation to measure the perceived status of health, a good point of view of patients' perspective is reached. In this study, the long-term physical functioning was poor among the amputees, but also among patients after both endovascular and surgical revascularization. Depressive symptoms might hinder these patients from effective reconditioning. (Studies III and IV)
5. During the data collection and the writing of the studies a clear lack of distinctly gathered information was noticed (Studies I and II).
6. Comprehensive assessment and regular use of QoL measures might help with the effectiveness of focusing on issues that have hindered a patient from reaching a better state of health and functional capacity otherwise aimed by skilful invasive procedures. A comprehensive assessment should be done before and perioperatively with major LEA in order to save a patient from too many LEAs, and for postoperative rehabilitation in order to offer a patient as good as possible quality of the rest of his or her life. The responsibility lies on the whole care chain. (Studies III and IV)

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APPENDICES

Appendix 1

PATIENT'S QUALITY OF LIFE

A lower leg peripheral arterial disease patient on target

Person to contact
Leena Remes
Specialist in Physiatry

The date of filling in the questionnaire:

Name:

Address:

Phone number:

Age:

Male: Female

Marital status: Married Cohabiting Widowed Divorced

How many people live in the same household with you?

Your former profession/ occupation

Your height …… cm Your weight ………..kg

List all your diseases you have here…………….

List all your daily medications you presently have …………………

Here are questions dealing with your health related quality of life.
Please, first read each items all response possibilities carefully. Then mark a cross (x) at the choice that describes your present health the most. Do so in all items 1 through 19, and items 26-29 in this manner. From each item pick only one alternative.

1

1) QUALITY OF LIFE QUESTIONNAIRE (15D©)

QUESTION 1. MOBILITY
1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

QUESTION 2. VISION
1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING
1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( ) I hear normal speech with a little difficulty.
3 ( ) I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
4 ( ) I hear even loud voices poorly; I am almost deaf.
5 ( ) I am completely deaf.

QUESTION 4. BREATHING
1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( ) I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING
1 ( ) I am able to sleep normally, i.e. I have no problems sleeping.
2 ( ) I have slight problems sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( ) I have moderate problems sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4 ( ) I have great problems sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

QUESTION 6. EATING
1 ( ) I am able to eat normally, i.e. with no help from others.
2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
3 ( ) I need some help from another person with eating.
4 ( ) I am unable to eat by myself at all, so I must be fed by another person.
5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

QUESTION 7. SPEECH
1 ( ) I am able to speak normally, i.e. clearly, audibly and fluently.
2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( ) I can make myself understood, but my speech is e.g. disjointed, faltering, stuttering or stammering.
4 ( ) Most people have great difficulty understanding my speech.
5 ( ) I can only make myself understood by gestures.

QUESTION 8. ELIMINATION
1 ( ) My bladder and bowel work normally and without problems.
2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhea.
4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
5 ( ) I have no control over my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES
1 ( ) I am able to perform my usual activities (e.g. employment, studying, housework, free-time activities) without difficulty.
2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( ) I can only manage a small proportion of my previously usual activities.
5 ( ) I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION
1 ( ) I am able to think clearly and logically, and my memory functions well
2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( ) I am permanently confused and disoriented in place and time.

QUESTION 11. DISCOMFORT AND SYMPTOMS
1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

QUESTION 12. DEPRESSION
1 ( ) I do not feel at all sad, melancholic or depressed.
2 ( ) I feel slightly sad, melancholic or depressed.
3 ( ) I feel moderately sad, melancholic or depressed.
4 ( ) I feel very sad, melancholic or depressed.
5 ( ) I feel extremely sad, melancholic or depressed.

QUESTION 13. DISTRESS
1 ( ) I do not feel at all anxious, stressed or nervous.
2 ( ) I feel slightly anxious, stressed or nervous.
3 ( ) I feel moderately anxious, stressed or nervous.
4 ( ) I feel very anxious, stressed or nervous.
5 ( ) I feel extremely anxious, stressed or nervous.

QUESTION 14. VITALITY
1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired or feeble.
3 ( ) I feel moderately weary, tired or feeble.
4 ( ) I feel very weary, tired or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY
1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.
3 ( ) My state of health has a considerable effect on my sexual activity.
4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible. 15D©/Harri Sintonen

QUESTION 16. DO YOU FEEL THAT YOUR LIFE AT PRESENT IS
1. very interesting,
2. fairly interesting,
3. fairly boring,
4. very boring?

QUESTION 17. DO YOU FEEL THAT YOUR LIFE AT PRESENT IS
1. very happy,
2. fairly happy,
3. fairly sad,
4. very sad?

QUESTION 18. DO YOU FEEL THAT YOUR LIFE AT PRESENT IS
1 very easy
2 fairly easy
3 fairly hard
4 very hard?

QUESTION 19. DO YOU FEEL THAT AT THE PRESENT MOMENT YOU ARE:
1. very lonely,
2. fairly lonely,
3. not at all lonely?

Weigh up your changes/possibilities to get help from your near ones, when you need help or support. You may mark one or several alternatives for each item if you feel like that.

QUESTION 20. WHO CAN YOU REALLY COUNT ON TO BE DEPENDABLE WHEN YOU NEED HELP?
1. Spouse or a companion
2. Other near relatives
3. A close friend
4. A close work mate
5. A close neighbor
6. Another close person
7. No one

QUESTION 21. WHO CAN YOU REALLY COUNT ON TO HELP YOU FEEL MORE RELAXED WHEN YOU ARE UNDER PRESSURE OR TENSE?

1. Spouse or a companion
2. Other near relatives
3. A close friend
4. A close work mate
5. A close neighbor
6. Another close person
7. No one

QUESTION 22. WHO ACCEPTS YOU TOTALLY, INCLUDING BOTH YOUR WORST AND YOUR BEST POINTS?

1. Spouse or a companion
2. Other near relatives
3. A close friend
4. A close work mate
5. A close neighbor
6. Another close person
7. No one

QUESTION 23. WHO CAN YOU REALLY COUNT ON TO CARE ABOUT YOU, REGARDLESS OF WHAT IS HAPPENING TO YOU?

1. Spouse or a companion
2. Other near relatives
3. A close friend
4. A close work mate
5. A close neighbor
6. Another close person
7. No one

QUESTION 24. WHO CAN YOU REALLY COUNT ON TO HELP YOU FEEL BETTER WHEN YOU ARE FEELING GENERALLY DOWN-IN-THE-DUMPS?

1. Spouse or a companion
2. Other near relatives
3. A close friend
4. A close work mate
5. A close neighbor
6. Another close person
7. No one

QUESTION 25. WHO CAN YOU COUNT ON TO CONSOLE YOU WHEN YOU ARE VERY UPSET?

1. Spouse or a companion
2. Other near relatives
3. A close friend
4. A close work mate
5. A close neighbor
6. Another close person
7. No one

QUESTION 26. IN GENERAL, WOULD YOU SAY YOUR HEALTH IS

1. Excellent
2. Very good
3. Good
4. Fair
5. Poor
6. How often have you experienced the following symptoms during the last passed month? Please, answer even though you haven't experienced any symptoms.

QUESTION 27. PALPITATION WITHOUT PHYSICAL EXERCISE

1. Daily or nearly daily
2. About weekly
3. More seldom
4. Not at all

QUESTION 28. IRREGULAR HEARTBEATS

1. Daily or nearly daily
2. About weekly
3. More seldom
4. Not at all

QUESTION 29. CHEST PAIN DURING ANGER OR OTHER KIND OF EMOTION

1. Daily or nearly daily
2. About weekly
3. More seldom
4. Not at all

QUESTIONS 30–39:

	Yes, limited a lot	Yes, limited a little	No, not limited at all
30. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
31. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
32. Lifting or carrying groceries	[1]	[2]	[3]
33. Climbing several flights of stairs	[1]	[2]	[3]
34. Climbing one flight of stairs	[1]	[2]	[3]
35. Bending, kneeling, or stooping	[1]	[2]	[3]
36. Walking more than a mile	[1]	[2]	[3]
37. Walking several blocks	[1]	[2]	[3]
38. Walking one block	[1]	[2]	[3]
39. Bathing or dressing myself	[1]	[2]	[3]

Estimate your average daily walking distance
Please, count up the distance you walk inside the house and outside approximately in meters/day: ______

QUESTIONS 40–43:

How **TRUE** or **FALSE** is each of the following statements for you.

(Circle One Number on Each Line)

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
40. I seem to get sick a little easier than other people	1	2	3	4	5
41. I am as healthy as anybody I know	1	2	3	4	5
42. I expect my health to get worse	1	2	3	4	5
43. My health is excellent	1	2	3	4	5

Geriatric Depression Scale: Short Form

Choose the best answer for how you have felt over the past week:
1. Are you basically satisfied with your life? ....YES / NO
2. Have you dropped many of your activities and interests? ....YES / NO
3. Do you feel that your life is empty? ....YES / NO
4. Do you often get bored? ....YES / NO
5. Are you in good spirits most of the time? ....YES / NO
6. Are you afraid that something bad is going to happen to you? ....YES / NO
7. Do you feel happy most of the time? ....YES / NO
8. Do you often feel helpless? ....YES / NO
9. Do you prefer to stay at home, rather than going out and doing new things? YES / NO
10. Do you feel you have more problems with memory than most? ....YES / NO
11. Do you think it is wonderful to be alive now? ....YES / NO
12. Do you feel pretty worthless the way you are now? ....YES / NO
13. Do you feel full of energy? ....YES / NO
14. Do you feel that your situation is hopeless? ....YES / NO
15. Do you think that most people are better off than you are? ....YES / NO

Have you ever smoked daily? Yes No
If you have quit smoking, so for how many years ago have you stopped? ____________
If you do smoke presently, how much do you smoke daily cigarettes? _________
pipefuls? __________
cigars? ____________

QUESTIONS 44. HOW OFTEN HAVE YOU BEEN DRUNK DURING THE PAST 12 MONTHS?

1. Not a single time
2. Once
3. 2-3 times
4. 4-5 times
5. About once every two months
6. About once a month
7. 2-3 times a month
8. About once a week
9. Twice a week or more often
10. Approximately how much/many of the following alcoholic drinks/beverage you have?

QUESTIONS 45. BEER PER WEEK?

1. Not at all
2. Less than a bottle (a´ 0,33 liters)
3. 1-4 bottles
4. 5-12 bottles
5. 13-24 bottles
6. 25-47 bottles
7. More than 48 bottles

QUESTIONS 46. WINE OR OTHER MILD ALCOHOLIC DRINKS PER WEEK?

1. Not at all
2. Less than a glass
3. 1-4 glasses
4. 1-2,5 bottles
5. 3-4,5 bottles
6. 5-9 bottles
7. More than 10 bottles

QUESTIONS 47. STRONG ALCOHOLIC DRINKS PER MONTH?

1. Not at all
2. Less than a half a bottle (a´ 0,5 liter)
3. A half – 1,5 bottles
4. 2-3,5 bottles
5. 4-9 bottles
6. 10-19 bottles
7. More than 20 bottles

QUESTIONS 48. HAVE YOU PASSED OUT WHILE USING ALCOHOL DURING THE LAST YEAR?

1. Not once
2. Once
3. 2-3 times
4. 4-6 times
5. 7 times, or more

Appendix 2

Quality of life, status of health and symptom screening scales used in the comparison between PAD patients and their age- and gender-matched controls:

Cardiac symptoms

There were three questions relating to cardiac symptoms: whether subjects had experienced daily or weekly a) chest pain during anger or another kind of emotion, b) palpitation without physical exercise, or c) irregular heartbeats, or not (Sumanen et al., 2004).

The 15D health-related QoL scale (15D HRQoL)

The 15D health-related quality of life instrument is a Finnish scale which reliability, validity, discriminatory power and responsiveness to change of its health state descriptive system and valuation system is described by Sintonen at the beginning of this century (Sintonen, 2001). It is generally accepted to also suit our kind of patient population and its comparison to age- and gender-matched controls (Koivunen et al., 2007).

In the 15D HRQoL12 out of 15 items had to be answered. Failure to do so resulted in the patient-control-pair being deleted from the HRQoL profile material.

The 6-item Brief Social Support Questionnaire (SSQ6)

The short form of the Sarason's social support score, SSQ6 has high internal validity (Sarason, 1987). The use of only the number part of score has been utilized in previous studies in Finland. They represent large populations (Elovainio et al., 2003; Vahtera et al., 2002; Väänänen et al., 2005; Väänänen et al., 2008).

Perceived social support was assessed using two measures: 1) the size of social network and 2) social network heterogeneity as set out in the 6-item Brief Social Support Questionnaire (SSQ6)

(Sarason, 1987). In this study, SSQ6 differentiated 0 to 6 sources of social support (options: spouse or companion /other close relative/friend/ close workmate /neighbour/another close person/'no one') in six different situations (for example, "Who can you count on to console you when you are very upset?") (Elovainio et al., 2003). 'The Satisfaction part' of SSQ6 was not used, only 'the Number part'; thus 36 was the maximum amount for social support. This value was divided by the number of items, 6, which gave the SSQ6 Number score (SSQ6N). The social network heterogeneity was analyzed by checking whether there was at least one time support from the spouse, or companion, other near relatives, a close friend, a close workmate, a close neighbour, another close person, or 'no one'. At least four items had to be answered in order to obtain the SSQ6 responses to the analysis, otherwise the respondent's answers were omitted.

The Physical Functioning and General Health subscales of the Rand-36 Item Health Survey 1.0 (Rand-36 PF and Rand-36 GH)

The Rand-36 HRQoL instrument has also been validated for the Finnish population and is also in Finnish (Aalto, 1999). All correlations between items and their hypothesized scales (corrected for overlap) are at least 0.50. Rand-36 PF and Rand-36 GH subscales of the Rand-36 Item Health Survey 1.0 scorings were run according to the instructions at
http://www.rand.org/health/surveys_tools/mos/mos_core_36item_scoring.html
In order for the respondent's sum score to be included, a minimum of 5/10 questions had to be answered in Rand-36 PF and 3/5 in Rand-36 GH subscale.

The Geriatric Depression Scale (GDS)

In the Geriatric Depression Scale (GDS) the use of the cut-off point 4/5 for the GDS-15 has produced sensitivity and specificity rates of 92.7% and 65.2% respectively, and positive and negative predictive values of 82.6% and 83.3% respectively when ICD-10 diagnostic criteria for major depressive episode have been used as the 'gold standard'. Reliability coefficients have been 0.81 for GDS-15. The optimum cut-off point for the GDS has been 10, yielding a sensitivity of 100% and a specificity of 84%. A shorter version of the GDS has had a sensitivity of 92% and a specificity of 81% using a cut-off point of 5. All scales lose accuracy when used to detect minor depression or the presence of any depressive diagnosis. (Almeida and Almeida, 1999)

In the 15 item Geriatric Depression Scale (Yesavage et al., 1982; Almeida and Almeida, 1999) from 0 to 15, a score of 5 points or more is suggestive of depression and ought to warrant a comprehensive follow-up assessment. A score of 10 points or more was considered indicative of depression. If respondents set their answer in between 'yes' or 'no', 0.5 points were allocated for the item in question. A minimum of 12/15 questions had to be answered. Failure to do so resulted in the respondent's summary score being deleted.

The Life Satisfaction score (LS)

Life Satisfaction Score's correlation coefficients between each item and the life satisfaction score range from 0.63 to 0.80 ($p < 0.001$). Cronbach's alpha was 0.74. Distribution of the life satisfaction score is skewed, with lower scores representing greater life satisfaction predominating irrespective of gender, health status, or age group. (Koivumaa-Honkanen, 1998)

Life Satisfaction was assessed using a series of four questions from a life-quality study conducted at the University of Michigan and adapted in the Finnish cohort study of twins (Allardt, 1973) (Koivumaa-Honkanen et al., 2000). Self-reported life satisfaction (LS) was measured using a four-question scale with sum score (LS, range 4–20) categorized as satisfied (LS: 4–6), intermediate (LS: 7–11) or dissatisfied (LS: 12–20). Participants were asked to rate four aspects of LS: interest in life, happiness, ease of living and loneliness (very interesting/happy/easy/not at all lonely=1, fairly interesting/happy/easy=2, missing data and `cannot say' = 3, fairly boring/unhappy/hard/lonely=4, very boring/unhappy/hard/lonely=5) (Koivumaa-Honkanen et al., 2000). At least two out four items had to be answered in order to get the sum score for the analysis otherwise the respondent's sum score was omitted.

'Perceived state of health'

'Perceived state of health' was taken separately from the Rand-36 *General Health* subscale (having been included in the study protocol as a whole) and studied according to Likert's five-step scale (good, quite good, fair, rather poor and poor). Due to small frequencies extreme categories were combined, and a three-step scale (good, fair, and poor) was used in the analyses.

Mini-Mental-State Examination

The cognition was measured by using Mini-Mental-State Examination (MMSE). One trained research assistant performed most of the MMSE tests on the participants. MMSE is an easy to use and commonly used test to evaluate cognitive capacity. It may not be used as a single test to detect dementia (Tombaugh and McIntyre, 1992). MMSE is not sensitive enough to detect mild cognitive impairment. The repeatability of the test is good (Juva et al., 1994)

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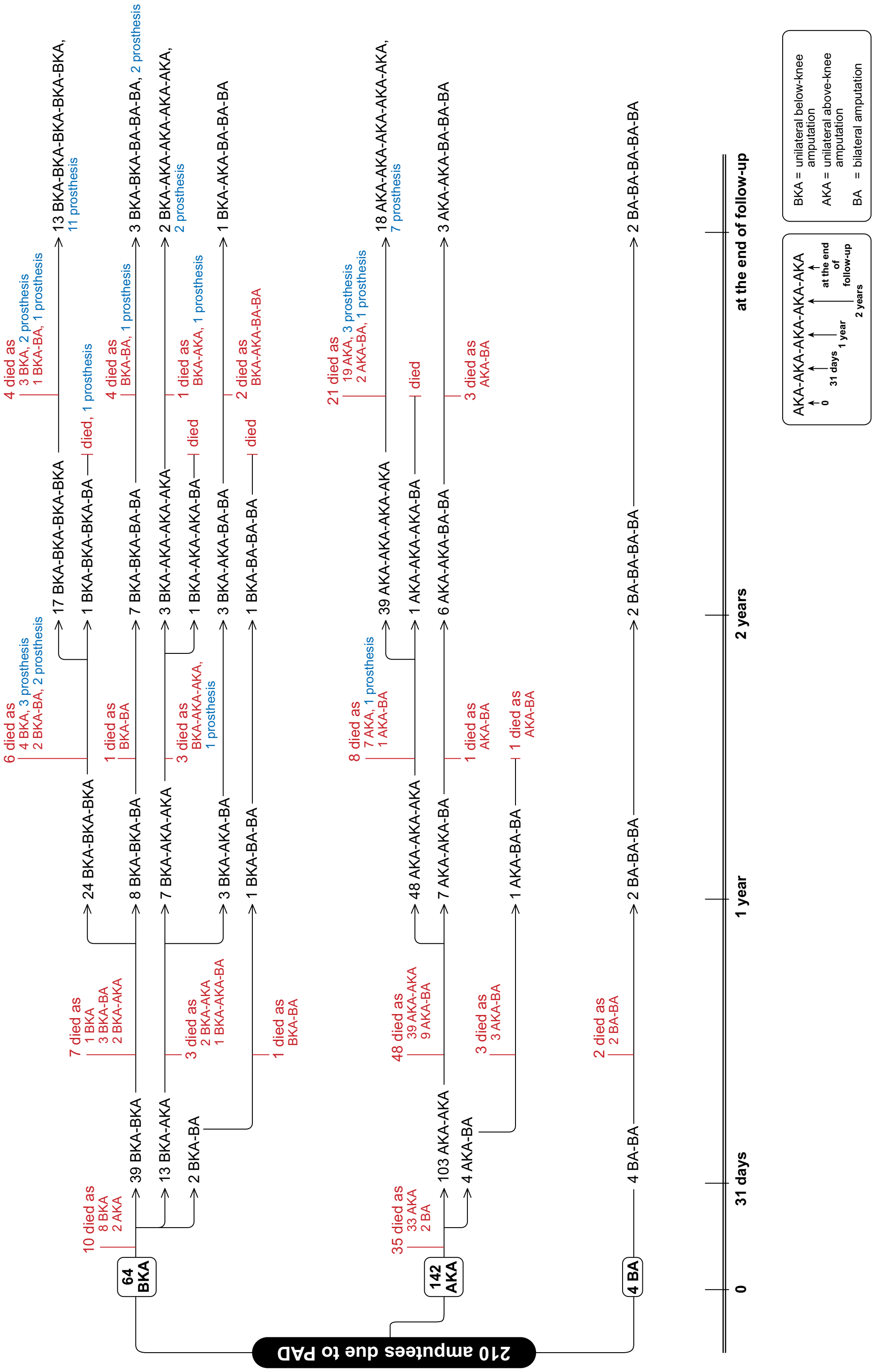
Appendix 3 The trajectories of the 210 amputees



Appendix 4 Revascularizations performed on the index amputated legs of the 210 amputees in Turku, in 1998-2002

Revascularization	Men(N=95)		Women(N=115)	
	n	%	n	%
PTA[1]	**20**	**21.1**	**29**	**25.2**
>1 year before amputation	2	2.1	4	3.5
<1 year and > ½ years before amputation	0	0.0	4	3.5
less than ½ year before amputation	18	19.0	21	18.2
No PTA performed	75	79.0	86	74.8
Y prosthesis	**7**	**7.4**	**1**	**0.9**
>1 year before amputation	7	7.4	0	0.0
less than ½ years before amputation	0	0.0	1	0.9
no Y prosthesis	88	92.6	114	99.1
Inguinal bypass other than Y prosthesis	**16**	**16.8**	**13**	**11.3**
>1 year before amputation	6	6.3	6	5.2
<1 year and > ½ years before amputation	2	2.1	1	0.9
less than ½ years before amputation	8	8.4	6	5.2
no inguinal bypass performed	79	83.2	102	88.7
Suprapopliteal bypass	**10**	**10.5**	**8**	**7.0**
>1 year before amputation	1	1.0	1	0.9
<1 year and > ½ years before amputation	2	2.1	1	0.9
less than ½ year before amputation	7	7.4	6	5.2
no suprapopliteal bypass performed	85	89.5	107	93.0
Infrapopliteal bypass	**2**	**2.1**	**2**	**1.7**
>1 year before amputation	0	0.0	0	0.0
<1 year and > ½ years before amputation	0	0.0	0	0.0
less than ½ year before amputation	2	2.1	2	1.7

Appendix 5 Revascularizations performed on the remaining leg of[1] the 210 amputees in Turku, in 1998-2002

Revascularization	**Men(N=95)**		**Women(N=115)**	
	n	%	n	%
PTA[2]	**9**	**9.5**	**11**	**9.6**
>1 year before amputation	6	7.4	5	4.4
<1 year and > ½ year before amputation	1	1.0	2	1.7
less than ½ year before amputation	2	2.1	4	3.5
no PTA performed	86	90.5	104	90.4
Y prosthesis	**7**	**7.4**	**1**	**0.9**
>1 year before amputation	7	7.4	0	0.0
less than ½ year before amputation	0	0.0	1	0.9
no Y prosthesis	88	92.6	114	99.1
Inguinal bypass other than Y prosthesis	**3**	**3.2**	**7**	**6.1**
>1 year before amputation	2	2.1	4	3.5
<1 year and > ½ year before amputation	0	0.0	1	0.9
less than ½ year before amputation	1	1.1	2	1.7
no inguinal bypass performed	92	96.8	108	93.9
Suprapopliteal bypass	**5**	**5.2**	**4**	**3.5**
>1 year before amputation	4	4.2	1	0.9
<1 year and > ½ year before amputation	0	0.0	0	0.0
less than ½ year before amputation	1	1.0	3	2.6
no suprapopliteal bypass performed	90	95.8	111	96.5
Infrapopliteal bypass	**0**	**0.0**	**2**	**1.8**
>1 year before amputation	0	0.0	1	0.9
<1 year and > ½ year before amputation	0	0.0	0	0.0
less than ½ year before amputation	0	0.0	1	0.9
no infrapopliteal bypass performed	95	100.0	113	98.2

[1]The revascularization was performed either before the index major amputation of the patient or after it.