Helsinki University, Institute of Clinical Medicine,
Department of Surgery, Vascular Surgery
∩
Department of Vascular Surgery
Helsinki University Central Hospital
Helsinki, Finland

AMPUTATIONS FOR CRITICAL LEG ISCHAEMIA -VASCULAR PREVENTION AND OUTCOME

Elina Eskelinen

Academic dissertation

Helsinki 2005

To be presented , with the assent of the Medical Faculty of the University of Helsinki,
for public examination in Auditorium 2 of the Meilahti Hospital, Helsinki University Central Hospital, Helsinki, Haartmaninkatu 4, on December 2nd, 2005, at 12 noon

Supervised by:

Professor Mauri Lepäntalo, MD
Vascular Surgery, Helsinki University
Chief of the Department of Vascular Surgery
Helsinki University Central Hospital
Helsinki, Finland

Reviewed by:

Docent Kimmo Mäkinen
University of Kuopio

and

Docent Timo Pohjolainen
University of Helsinki

Discussed with:

Docent Fausto Biancari
University of Oulu

ISBN 952-91-9455-2 (paperback)
ISBN 952-10-2755-X (PDF)

Tampere 2005
Tampereen yliopistopaino Oy Juvenes Print

1. CONTENTS

2. LIST OF ORIGINAL ARTICLES

This thesis is based on the following original articles, which are referred to in the text by their Roman numerals:

I E. Eskelinen, A. Eskelinen, T. Hyytinen, A. Jaakkola. Changing pattern of major lower limb amputations in Seinäjoki Central Hospital 1997-2000. Annales Chirurgiae et Gynaecologiae 2001; 90: 290-293.

II E. Eskelinen, M. Lepäntalo, E-M Hietala, H. Sell, L. Kauppila, I. Mäenpää, J. Pitkänen, P. Salminen-Peltola, S. Leutola, A. Eskelinen, A. Kivioja, E. Tukiainen, A. Lukinmaa, P. Brasken, M. Railo. Lower limb amputations in Southern Finland in 2000 and trends up to 2001. European Journal of Vascular and Endovascular Surgery 2004; 27: 193-200.

III E. Eskelinen, M. Luther, A. Eskelinen, M. Lepäntalo. Infrapopliteal bypass reduces amputation incidence in elderly patients: a population-based study. European Journal of Vascular and Endovascular Surgery 2003; 26: 65-68.

IV E. Eskelinen, A. Albäck, W-D. Roth, K. Lappalainen, P. Keto, M. Railo, A. Eskelinen, M. Lepäntalo. Infrainguinal percutaneous transluminal angioplasty for limb salvage: a retrospective analysis in a single center. Acta Radiologica 2005; 46: 155-162.

V E. Eskelinen, A. Eskelinen, A. Albäck, M. Lepäntalo. Major amputation incidence decreases both in non-diabetic and in diabetic patients in Helsinki. (submitted).

3. ABBREVIATIONS

ABI	ankle brachial pressure index
AK	above knee
APS	antiphospholipid antibody syndrome
BK	below knee
BK/AK	below knee / above knee-ratio
CAD	coronary artery disease
CLI	critical leg ischaemia
CRP	C-reactive protein
CVD	cerebrovascular disease
DM	diabetes mellitus
HUCH	Helsinki University Central Hospital
IC	intermittent claudication
IPBS	infrapopliteal bypass surgery
PAD	peripheral arterial disease
PTA	percutaneous transluminal angioplasty
SCS	spinal cord stimulation
TAO	thromboangiitis obliterans
TASC	Trans Atlantic Consensus Document
WHO	World Health Organisation

4. ABSTRACT

Introduction: There is an ongoing controversy as to whether there has been a significant reduction in amputations and by what means amputations are avoided in patients with critical leg ischaemia.

Aims of the present study: The aim of this study was to evaluate the incidence of major amputation and the outcome of amputees in two well defined areas and the association between revascularisation and amputation.

Methods:

1. The outcome of 169 major lower limb amputations during the period 1997-2000 in the Seinäjoki Central Hospital region (area I) was investigated retrospectively. The annual incidence of major amputation was assessed.
2. The outcome of 215 major lower limb amputations in 2000 in Southern Finland (area II) was reviewed retrospectively. The annual incidence of major amputation and infrainguinal (or infrapopliteal) bypass during the period 1990-2001 was assessed.
3. A nation-wide study was undertaken to analyse retrospectively data on infrapopliteal bypasses and major amputations for patients aged $\geq$ 70 years with critical leg ischaemia. Hospital regions were divided into two equal groups according to the numbers of infrapopliteal bypasses performed on patients aged $\geq$ 80 years.
4. The outcome of 230 critically ischaemic limbs treated with infrainguinal percutaneous transluminal angioplasty at Helsinki University Central Hospital during the period 2000-2002 were analyzed retrospectively.
5. The clinical records of 1094 patients who underwent major lower limb amputation for vascular disease in Helsinki during the period 1990-2002 were analyzed retrospectively. The study period was divided into three parts (1990-1994, 1995-1998 and 1999-2002) and results were compared between diabetic and nondiabetic vascular amputees for each part.

Results:

1.The incidence of major lower limb amputation (lost legs) in 2000 was 152 (I) and 135 (II) per million inhabitants respectively in the two areas studied.

2. In study area II, the decrease in amputation incidence over the period 1990-2000 was 25% and the decrease in age-adjusted amputation incidence 30%. Over this period there was a significant inverse correlation between incidence of infrainguinal bypass and amputation (r=-0.682, p=0.021) and between incidence of infrapopliteal bypass and amputation (r=-0.682, p=0.021).

3. The incidences of major amputation in the active group (978 bypasses per million inhabitants) and passive group (57 per million) were 1976 and 3177 per million respectively (p=0.016). There was a significant (p=0.012) inverse relationship between the numbers of infrapopliteal bypass operations and major amputations in patients aged ≥ 80 years.

4. In the series of patients with critical leg ischaemia treated with percutaneous transluminal angioplasty, primary patency, secondary patency, limb salvage and survival rates were 47%, 59%, 92% and 76% respectively at 12 months.

5. The overall incidence of major amputations in diabetics and nondiabetics decreased by 23% and 40% respectively from the first period (1990-1994) to the last (1999-2002).

Conclusions:

1. Active revascularisation saves legs from major amputation.

2. Infrapopliteal bypass can be considered as an index-procedure in preventing major amputations.

3. A decrease in amputation rates among elderly patients can be achieved at least as well as in younger patients by means of active revascularisation.

4. Percutaneous transluminal angioplasty can be considered as a first-line treatment in a selected group of patients with critical leg ischaemia, as it gives good limb salvage rates.

5. The decrease in major amputation rates among diabetic as well as nondiabetic patients can be attributed to the increased interest in amputation prevention.

5. INTRODUCTION

The definition of a lower extremity amputation is the complete loss of any part of the lower limb for any reason. A major amputation is defined as an amputation proximal to the tarsometatarsal joint and a minor amputation as one (through or) distal to this joint (Group TG 2000). In practice, the most important landmark is the heel, and therefore major amputations are those above heel level. As very few amputations are of Lisfranc, Chopart or Syme type (Solonen 1991), these two approaches distinguish almost the same groups of patients. For the patient, there is a vast difference between minor and major amputations: minor amputations do not restrict function and mobility as major amputations do. Thus, these two amputation types should be reported separately.

The majority of major lower limb amputations are currently performed for critical leg ischaemia (CLI) (Alaranta et al. 1995; Ebskov 1992; Group TG 2000; Laaperi et al. 1993; Pohjolainen and Alaranta 1988; Pohjolainen and Alaranta 1999). Treatment of CLI is one of the most important tasks of vascular surgery, and it accounts for a major part (35%) of vascular surgical activity in Finland (Luther et al. 2000). One of the main goals in vascular surgery is to obviate the need for major amputation. From the vascular surgeon´s point of view, only major amputations count as possible treatment failures, and only if the leg was salvageable by some means of revascularisation (Lepantalo et al. 2000). Nonambulatory patients, who require a stable, pain-free limb, and institutionalised patients and those with terminal co-morbid conditions will gain no benefit from revascularisation procedures (Biancari et al. 2000; Humphreys et al. 1995; Johnson et al. 1995). Whatever the decision, all potentially ambulant patients with CLI should be seen by a vascular surgeon before amputation is recommended (Lepantalo et al. 2000; Shearman et al. 2000; Wahlberg et al. 1994).

Treatment stategies for CLI still vary greatly, in Finland and elsewhere (Bradbury et al. 2002; Luther et al. 2000). The same patients may receive entirely different treatment depending on which hospital they attend (Bradbury et al. 2002). The role of percutaneous transluminal angioplasty (PTA) in treating CLI patients has become an issue of increasing interest, but also a source of controversy (Bradbury et al. 2002; Bradbury and Ruckley

1996). To ascertain the appropriate treatment methods for CLI, more data on different treatment strategies is needed. The aim of this study was to seek this information.

6. REVIEW OF THE LITERATURE

6.1 Etiology of lower limb major amputations

Vascular causes account for the majority of major lower limb amputations performed in the Western world during peacetime (Alaranta et al. 1995; Ebskov 1992; Group TG 2000; Laaperi et al. 1993; Pohjolainen and Alaranta 1988; Pohjolainen and Alaranta 1999). Lower-limb amputations performed for other reasons, such as trauma or tumour, have decreased in significance. The main causes of lower limb amputations and the proportion of different diagnoses are listed in Table 1 (Alaranta et al. 1995; Ebskov 1992; Group TG 2000; Laaperi et al. 1993; Pohjolainen and Alaranta 1988; Pohjolainen and Alaranta 1999; Rommers et al. 1997; Wahlberg et al. 1994; Witso and Ronningen 2001).

Table 1. The main causes of major lower limb amputation.

Cause	% of amputations
Chronic critical leg ischaemia	70 - 90
Acute ischaemia	2.7 - 4.9
Diabetes mellitus	23 - 80
Tumour	1.5 - 3
Trauma	2 - 7
Miscellaneous	8 - 11

6.1.1 Nonvascular causes

Among traumatic lower limb major amputations, blunt injury, pulseless extremity, need for arterial repair (rather than ligation or no therapy), increasing number of injured tibial vessels and multiple long-bone fractures are predictors of amputation. Distal vascular injuries combined with complex orthopaedic fractures are more likely to result in limb loss (Moniz et al. 1997). The majority of all trauma-related amputations are performed on males (Ebskov et al. 1994; Pezzin et al. 2000).

In Finland, trauma caused 12% of all amputations in 1970 (Solonen and Huittinen 1991), whereas in 1984-85 and 1995 the corresponding figures for Southern Finland were 2% and 4% respectively (Pohjolainen and Alaranta 1999). In a multicenter study, the proportion of all major amputations associated with trauma was found to vary between 4% and 10% in Europe and North America (Group TG 2000). However, one exception to this was Newcastle, UK, where 15% of major amputations in women were associated with trauma. The decrease in the number of amputations due to trauma may be largely explained by improved industrial safety, improved methods of treatment of open fractures and by advances in vascular and replantation surgery (Ebskov 1994; Ostrup and Vilkki 1986; Pohjolainen and Alaranta 1988).

The treatment of primary tumours, particularly osteosarcoma, has changed over the past decades in terms of both medical and surgical care (Sweetnam 1991). About fourty years ago, the majority of patients were treated by amputation (Sweetnam 1969; Sweetnam et al. 1971), but the increasing number of cases treated by wide excision and the use of adjuvant chemotherapy have decreased the number of amputations (Grimer et al. 2002; Kavanagh et al. 1990; Sweetnam 1991). Despite the increase in the number of malignant melanomas localised in the lower extremities, the annual number of major lower limb amputations caused by this has remained constant (Ebskov 1993).

Deep infection, with or without concomitant vascular disease, usually affects diabetics. Limb-threatening infection carries a 25% risk of major amputation (Gibbons 1987). Approximately 1-4% of all major amputations are performed for deep infection without knowledge of underlying critical leg ischaemia (CLI) (Benotmane et al. 2000). Osteomyelitis without CLI caused 6 of 705 major amputations in Southern Finland during the period 1984-85 (Pohjolainen and Alaranta 1988).

Other causes, such as congenital deformity and frostbite, account for a minimal percentage of amputations (Alaranta et al. 1995; Laaperi et al. 1993; Pohjolainen and Alaranta 1988; Pohjolainen and Alaranta 1999). In less-recent data in particular, the proportion of ischaemia might have been underestimated due to the lack of systematic use of non-invasive vascular diagnostics (Burgess and Matsen 1981).

6.1.2 Atherothrombotic and other vascular causes

6.1.2.1 Atherothrombotic disease

Atherothrombotic arterial disease is a systemic disease affecting, in principle, all of the arterial tree, with the predominance of carotid, coronary and lower limb vessels. The clinical manifestations of atherosclerosis in different organs have been reported to occur with different frequencies, but always with considerable overlap (Aronow and Ahn 1994; CAPRIE Steering group 1996) (Figure 1). Chronic leg ischaemia is a gradually developing process giving rise to symptoms caused by a reduced arterial blood flow. With worsening flow, asymptomatic disease can progress through work-related pain to rest pain and tissue loss. Claudication caused by relative arterial insufficiency has a benign prognosis with low risk of limb loss, although mortality due to other atherosclerotic manifestations is high (Bloor 1961; Dormandy et al. 1999d). In the historical study by Bloor and co-workers during the period 1947-1953, critical leg ischaemia developed in 8.3% and 3.0% of the claudicants in the first and third years respectively after diagnosis. Of these critically ischaemic patients, 23-57% required major amputation (Bloor 1961). According to a recent review by Dormancy and colleagues, only 1-3% of claudicants ever require major amputation over a 5-year period (Dormandy et al. 1999d). Interestingly, it has been demonstrated that a third of patients with CLI have no preceding claudication (Matzke and Lepantalo 2001).

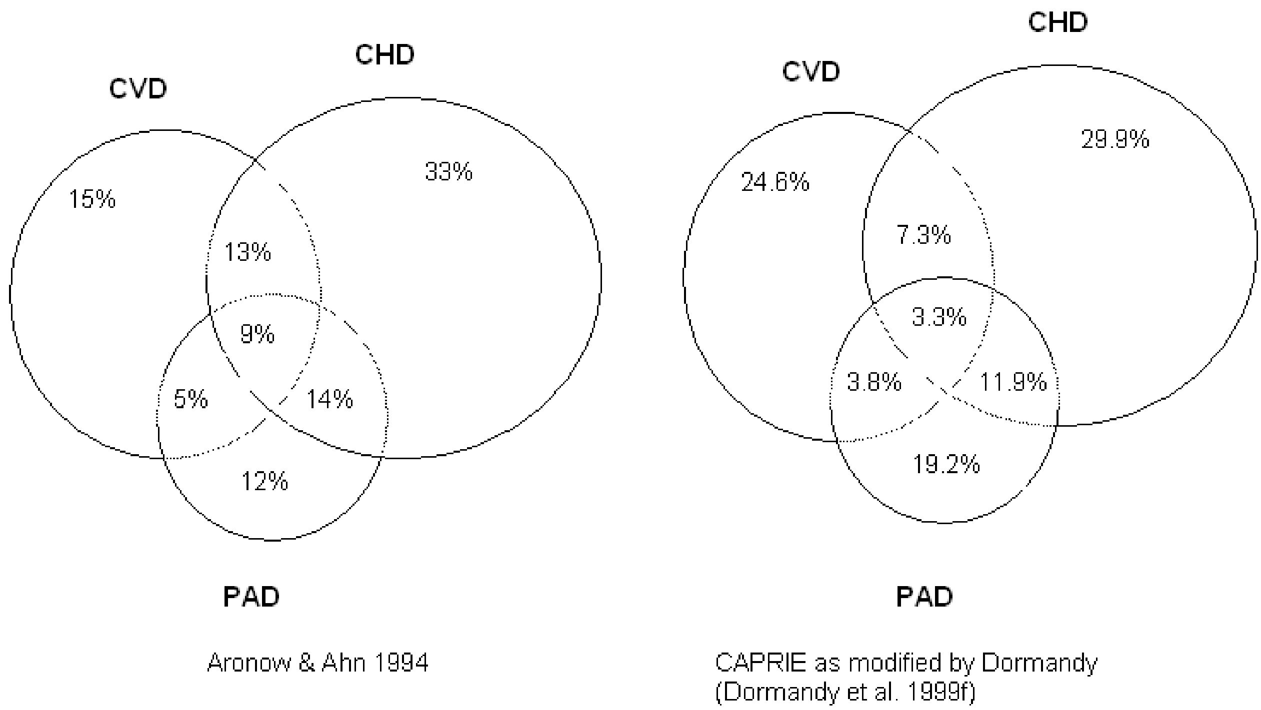


Figure 1. Distribution of the three main manifestations of occlusive arterial disease.
CVD= cerebrovascular disease, CHD= coronary heart disease, PAD= peripheral arterial disease.

6.1.2.2 Critical leg ischaemia

Atherosclerosis in the large arteries is the fundamental process in the pathogenesis of CLI. Reduced arterial blood flow in a limb causing rest pain or tissue loss (ulcerations or gangrene) represent CLI. CLI, with or without diabetes mellitus, accounts for 70-90% of lower limb amputations (Group TG 2000; Pohjolainen and Alaranta 1988) and is a growing problem in an ageing population demanding increasing vascular surgical resources (Luther 1994).

In 10-40% of cases CLI leads to primary amputation (Dormandy et al. 1999b; Lepantalo and Matzke 1996). As the outcome of CLI is so poor, the European Consensus Document recommends revascularization for the treatment of CLI if there is more than a 25% chance of patient survival and limb salvage for one year (Second European Consensus Document 1992).

Although not substantiated by an adequate prospective study, the presence of gangrene and ulceration (Fontaine IV) seems to be associated with a poorer prognosis than rest pain alone (Fontane III) (European Consensus Document on CLI 1990). In the study by the Joint Vascular Research Group in Britain (Wolfe 1986), patients with CLI who had gangrene or ulceration were twice as likely to require a major amputation than those with rest pain alone. Juergens and co-workers (Juergens et al. 1960) noted a 5-fold increase in a similar group over a 5-year period. In their series of 465 patients the incidence of major amputation was 19.8% for patients with ulcers or gangrene versus 3.8% for patients with rest pain only. In patients with gangrene it has been assumed that almost all patients will undergo amputation unless the circulation can be improved enough to achieve healing (Luther 1997).

6.1.2.3 Acute ischaemia

Acute ischaemia requiring lower extremity amputation results most frequently from either arterial thrombosis or embolism. The rare causes of acute lower limb ischaemia may be related to anatomic causes, vasculitis, drugs, trauma and iatrogenic reasons (Lepantalo et al. 2005). Despite the widespread use of the Fogarty thrombectomy catheter (Fogarty et al. 1963), arterial bypass (Yeager et al. 1992) and catheter-directed thrombolytic infusions (Ouriel 1996; Ouriel et al. 1994), the limb loss rate after acute ischaemia remains between 9% and 40% and mortality rates are up to 18% (Dormandy et al. 1999a; Kuukasjarvi and Salenius 1994; Ouriel 1996; Yeager et al. 1992).

6.1.2.4 Other vascular causes

Buerger´s disease (thromboangitis obliterans, TAO), although rare, is a clinical entity which affects mostly young, male, inveterate tobacco smokers who present with distal extremity ischaemia. The incidence of TAO is estimated to be 8-12/100 000 in North America (Cooper et al. 2004). Patients with Buerger´s disease often suffer from severe ischaemic pain and tissue loss culminating in major amputation in 12-30% of patients (Cooper et al. 2004; Mills 2003; Mills et al. 1987; Shigematsu and Shigematsu 1999; Van Damme et al. 1997). The risk of major amputation in TAO-patients is reported to be 11% and 23% at 5 and 20 years respectively (Cooper et al. 2004). Vasculitis, such as Takayasu´s disease and giant cell arteritis, leading to major amputation is extremely rare in Finland (Johnston et al. 2002; Le Hello et al. 2001; Lepantalo et al. 2005; Vanoli et al. 2001).

6.2 Critical leg ischaemia

6.2.1 Definition of CLI

Chronic leg ischaemia is a gradually developing process giving rise to symptoms caused by a reduced arterial blood flow. It is generally agreed that in critical leg ischaemia the viability of the leg is endangered unless some improvement of the arterial supply is undertaken, even if not all patients require major amputation. The Fontaine classification of ischaemia defines four stages based on clinical symptoms (Fontaine et al. 1955). Stages three and four, rest pain and tissue loss (ulcers or gangrene), represent the critical ischaemic stage (Second European Consensus Document 1992). However, not all patients with rest pain, ulcers or gangrene are under immediate threat of leg loss. Therefore, more precise criteria for critical leg ischaemia have been developed. They are based on both symptoms and objective pressure measurements as presented in Table 2. (Ad Hoc Committee 1986; Rutherford et al. 1997; Second European Consensus Document 1992).

Table 2. Criteria for chronic critical leg ischaemia.

	ankle pressure		*toe pressure*		*Symptoms*
European criteria (Eur cons doc 1992)	≤ 50 mmHg	or	≤ 30 mmHg	with	rest pain, ulcer or gangrene
Criteria of the Ad Hoc Committee	< 40 mmHg	or	< 30 mmHg	with	Rest pain
(Rutherford 1997)	< 60 mmHg	or	< 40 mmHg	with	Minor or major Tissue lost

These definitions produce a more objective tool for research purposes but at present no definition criteria are able to correctly identify all limbs threatened by CLI. The problem in defining critical leg ischaemia partly explains differing results achieved in the treatment of CLI-patients. Additionally, each definition criterion has been questioned and challenged mainly on the grounds that no definition has appeared to with any certainty predict the fate of an individual patient regarding limb survival in the absence of active treatment (Lundberg 2005).

6.2.2 Incidence and prevalence of CLI

Information on the incidence of CLI is sparse. CLI is difficult to assess on a population basis, therefore all calculations are based on different assumptions and projections.

Catalano (Catalano 1993) assessed CLI incidence in Italy using three different methods. The results from the three approaches were substantially equivalent in order of magnitude, giving the CLI incidence in a population aged over 45 as 450-652/million/year (Table 3).

Table 3. Incidence of critical leg ischaemia according to Italian data (Catalano 1993)

	Annual incidence (per million inhabitants)		
Population > 45 yrs	CLI	Major amputations	Amputations
7-year follow-up of claudicants	450		112
Sample of hospital in Lombardy	652		160
Amputations in Lombardy	577	146	172
Amputations in Emilia Romagna	530	133	154

The Vascular Surgical Society of Great Britain concluded, based on the reports of a national survey, that the annual incidence of CLI would be 400/million/year (The Vascular Surgical Society of Great Britain and Ireland 1995).

The incidence of CLI can also be extrapolated from the better-documented prevalence studies of intermittent claudication (IC). These calculations are based on the assumptions that occlusive arterial disease progresses from asymptomatic disease to claudication and from claudication to rest pain and eventually to tissue loss. If one assumes that the overall prevalence of claudication is 3% and that 5% of patients with IC will develop CLI over 5 years, this gives an incidence of CLI of 300/million/year (TASC 2000). These estimates, however, exclude those asymptomatic patients who never experience claudication but develop CLI (Dormandy et al. 1999d; Matzke and Lepantalo 2001). In a multicenter study in Italy, 14% of critically ischaemic patients presented without preceding symptoms of claudication (ICAI 1997). Therefore, the figures for prevalence or incidence calculated from the prevalence of claudication appear to be too low.

According to the TASC-document (TASC 2000), the CLI incidence can be calculated from the number of major amputations. Assuming that 90% of major amputations are performed for ischaemia and that only 25% of patients with CLI ever require a major amputation, it can be calculated that the incidence of CLI is approximately 500 to 1 000/million/year.

According to a review covering 21 studies, the incidence varied 10-fold, with predictions of 100-1000/million/year (Heikkinen 2003).

Apart from the Italian and English studies mentioned above, there are no direct data on the prevalence of CLI, but most cases either resolve or lead to amputation within a year, and therefore the incidence and prevalence are similar. The Vascular Surgical Society of Great Britain and Ireland suggested a prevalence of 400/million (1 in 2500) of the population annually (The Vascular Surgical Society of Great Britain and Ireland 1995).

6.2.3 Risk factors

The risk factors for the development of CLI are largely the same as the risk factors for peripheral arterial disease (PAD), although with a different weight of importance. The most important risk factors for CLI are age, diabetes and smoking. Risk factors may contribute to operative complications and influence patency, leg salvage and survival.

6.2.3.1 Age

The prevalence of PAD increases rapidly with age (Criqui et al. 1985; Luther 1994; TASC 2000). Age is also associated with the progression of PAD to CLI (Dormandy et al. 1999e; Murabito et al. 1997; Reunanen et al. 1982) as well as leg salvage and survival (Zdanowski et al. 1998). Vascular surgeons are facing an ever-increasing number of aged patients with CLI (Pomposelli et al. 1998). Major amputations are also more common in the elderly (Group TG 2000; Liedberg and Persson 1983; Luther 1994; Pohjolainen and Alaranta 1988). There is clear evidence that, despite shorter life expectancy and worse general condition (Hearn et al. 1996; Nehler et al. 1993), even octogenarians can undergo infrapopliteal bypass surgery (IPBS) safely, achieving graft patency and limb salvage rates that are comparable to those achieved in younger patients (Luther and Lepantalo 1997a; Luther and Lepantalo 1997b; Pomposelli et al. 1998). Several other authors also propose an active reconstruction policy in elderly patients (Esato et al. 1993; Gouny et al. 1994; Illuminati et al. 2000; Illuminati et al. 1999; Matsubara et al. 2001; McLoughlin et al. 1989; Nehler et al. 1993; O'Mara et al. 1987; Scher et al. 1986).

In a Finnish study analysing the outcome of femoropopliteal reconstructions for CLI, the percentage of patients achieving leg salvage up to three years or until death was similar in CLI patients younger than 70 and in those over 70 years of age (Luther and Lepantalo 1996). In another study (Luther and Lepantalo 1997b) femorotibial reconstructions for CLI were analysed. Neither increase in operative mortality nor any negative influence of age in patency, leg salvage or survival was found.

To evaluate the effectiveness of arterial reconstructive treatment on CLI it is essential to evaluate its impact on amputation rates in the population. With an increasing proportion of patients with critical ischaemia in the age group of 80 or more years, it is important to determine separately if results in the oldest age group justify an active reconstruction policy.

6.2.3.2 Diabetes

Foot ulcers are a major problem in diabetes, affecting approximately 15% of all diabetics during their lifetime (Gibbons and Eiopoulos 1995). Neuropathy seems to be the primary factor provoking foot ulceration in diabetics, but lower limb ischaemia is the major factor preventing wound healing (Lepantalo et al. 2000). The proportion of diabetic people among individuals suffering from CLI is increasing. According to the 7-year data of a nationwide vascular registry, Finnvasc, of 8250 patients treated for chronic critical leg ischaemia, 4070 had diabetes. Their proportion increased from 46% in 1991 to 51% in 1997 (Mätzke 2004). Diabetic patients account for 40-70% of all lower extremity amputations (Group TG 2000; International Consensus on the Diabetic Foot 1999) and diabetes carries some 10-fold risk for amputation (Da Silva et al. 1996; Luther 1997; Morris et al. 1998). On average, diabetics have to undergo amputation earlier than nondiabetics (Morris et al. 1998). The majority of all diabetes-related major lower limb amputations occur in patients with type II diabetes (Morris et al. 1998). The correlation between diabetes and major amputation rates is independent of other risk factors, including age and smoking (The Vascular Surgical Society of Great Britain and Ireland 1995). However, smoking does appear to have an additive effect (Pell and Fowkes 1997).

6.2.3.3 Smoking

Cigarette smoking increases both the risk of developing PAD and its progression (Da Silva et al. 1979; Liedberg and Persson 1983). The risks associated with smoking apply to all ages and increase with the number of cigarettes smoked (TASC 2000). Smoking is present as a risk factor for CLI in 33-92% of all patients (Luther 1997). In multivariate analyses too, smoking has been shown to be an independent risk factor (Liedberg and Persson 1983; TASC 2000). Major amputation is more common among patients with intermittent claudication (IC) who are heavy smokers and who continue to smoke (Juergens et al. 1960; TASC 2000), the difference being as striking as 11% in smokers and 0% in non-smokers within a 5-year study period (Juergens et al. 1960). In the Swedish study there were considerably more current smokers among amputees than among age-and sex-matched controls, and smokers had a much lower mean age at amputation (Liedberg and Persson 1983).

6.2.3.4 Gender

Generally, men have a higher prevalence of PAD than women, with an overall male/female ratio of 1.27 (Criqui 2001; Criqui et al. 1985). The female advantage disappears after menopause (Kroger et al. 1999), as females are reported to develop PAD at older age than males (Kannel and McGee 1985; Kroger et al. 1999; McDermott et al. 2003). Female gender combined with diabetes has been observed to be associated with an adverse outcome of revascularisation procedures in terms of graft patency and leg salvage (Luther and Lepantalo 1997b).

6.2.3.5 Renal Insufficiency

Chronic renal failure is associated with an increased risk of development of atherosclerosis and its complications. Patients with end-stage renal disease have poor long-term survival, with one and three-year survival rates of 72% and 39% respectively. (Harrington et al. 1990) Patients on long-term dialysis have a two-year survival rate of 23% (Biancari et al. 2002). Leg salvage, on the contrary, can achieve good results in patients with renal insufficiency (Harrington et al. 1990; Korn et al. 2000; Peltonen et al. 1998), especially patients in whom adequate autologous conduit is available (Meyerson et al. 2001). However, as patient survival is poor for dialysis patients, a selective approach to revascularisation in these patients is recommended (Harrington et al. 1990; Korn et al. 2000; Peltonen et al. 1998). In a study by Biancari et al (Biancari et al. 2002) the amputation-free survival of CLI-patients on long-term dialysis and with coronary artery disease was only 12% at one year and nil at two years. Therefore, in the presence of coronary artery disease in dialysis patients, infrainguinal revascularisation hardly appears to be indicated (Biancari et al. 2002).

6.2.3.6 Other cardiovascular manifestations

As the risk factors for PAD are similar to those for coronary artery disease (CAD) and cerebrovascular disease (CVD), patients with PAD also have a high prevalence of CAD and CVD as co-morbidities, although the extent of co-morbidity depends on the sensitivity of assessment (Criqui 2001). CAD is present in 31-75%, hypertension in 37-90% and CVD in 5-25% of patients with CLI (Luther 1997). The main reasons for premature death of CLI patients are the other manifestations of atherothrombotic disease, which cover 75% of deaths of CLI patients (Dormandy et al. 1999b): CAD in 40-60%, CVD in 10-20% and ruptured abdominal aortic aneurysm in 10% of cases (Luther 2003).

6.2.3.7 Infection

Limb-threatening infections should be treated immediately and aggressively with antibiotics, debridement and adequate drainage (LoGerfo and Marcaccio 1992). Ischaemic tissue, especially in diabetics, is optimal ground for infections. Infection, on the other hand, leads to microthrombus formation and thereby worsens the ischaemia by causing tissue necrosis (Lepantalo et al. 2000). Aggressive treatment of infection with broad-spectrum antibiotics and drainage is essential to prevent leg loss (Estes and Pomposelli 1996). Biancari and colleagues (Biancari et al. 1999) have calculated that patients undergoing a pedal bypass procedure with a serum level of C-reactive protein (CRP) above or equal to 100 mg/l have about a two-fold increase in risk for limb loss at one year. One important factor is prompt patient referral: as many as 25-31% of eventual amputees may present very late to the vascular surgeon with extensive gangrene or infection that precludes limb salvage (Abou-Zamzam et al. 2003; Wahlberg et al. 1994).

6.2.3.8 Hyperlipidaemia

The role of hyperlipidaemia as a factor associated with the development of PAD and its progression has not gained the same interest as in cardiac or neurologic assessment (Donnelly and Yeung 2002). The clinical management of peripheral vascular diseases should include prevention of secondary cardiovascular complications, (e.g. assesment of blood lipoprotein levels) which are often due to atherosclerotic plaque rupture leading to thrombotic vessel occlusion (Donnelly and Yeung 2002). A dyslipidaemic serum profile, characterisied by increased lipoprotein levels (Dionyssiou-Asteriou et al. 2000) and decreased HDL-cholesterol levels (Dionyssiou-Asteriou et al. 2000; Fowkes et al. 1992), has been shown to be associated with PAD. Two studies (Marcoux et al. 1996; Smith et al. 1996) have shown that, in multivariate analysis, hypertriglyceridaemia ($\geq$ 2.2 mmol/l) was the only independent factor associated with deterioration of ankle-brachial pressure index (ABI) and with the onset of CLI.

6.2.3.9 Thrombophilia

Thrombophilia may be defined as the tendency to arterial or venous thrombosis. Thrombophilia can be acquired or hereditary. With regard to arterial thrombosis, certain thrombophilic disorders have a definite pathophysiological role (Bohm and Al-Khaffaf 2003; Burns et al. 2001; Vig et al. 2004). Hyperhomocysteinaemia, inherited or acquired, has been demonstrated to be an independent risk factor for athero-thrombosis. The antiphospholipid antibody syndrome (APS), an acquired condition, strongly predisposes to arterial thrombosis. Other thrombophilic conditions, such as prothrombin gene G20210A variant or factor V Leiden, have been investigated, but current evidence does not unequivocally support the hypothesis of a pathophysiological role in athero-thrombosis (Bohm and Al-Khaffaf 2003). The risk of thrombotic occlusion following arterial revascularisation in patients with an identified thrombophilia defect appears to be almost three times that of patients with no evidence of a thrombophilia defect (Vig et al. 2004).

Figure 2 summarises the features that predispose to the development of CLI and gives an approximate risk assessment as illustrated by Dormandy et al (Dormandy et al. 1999e).

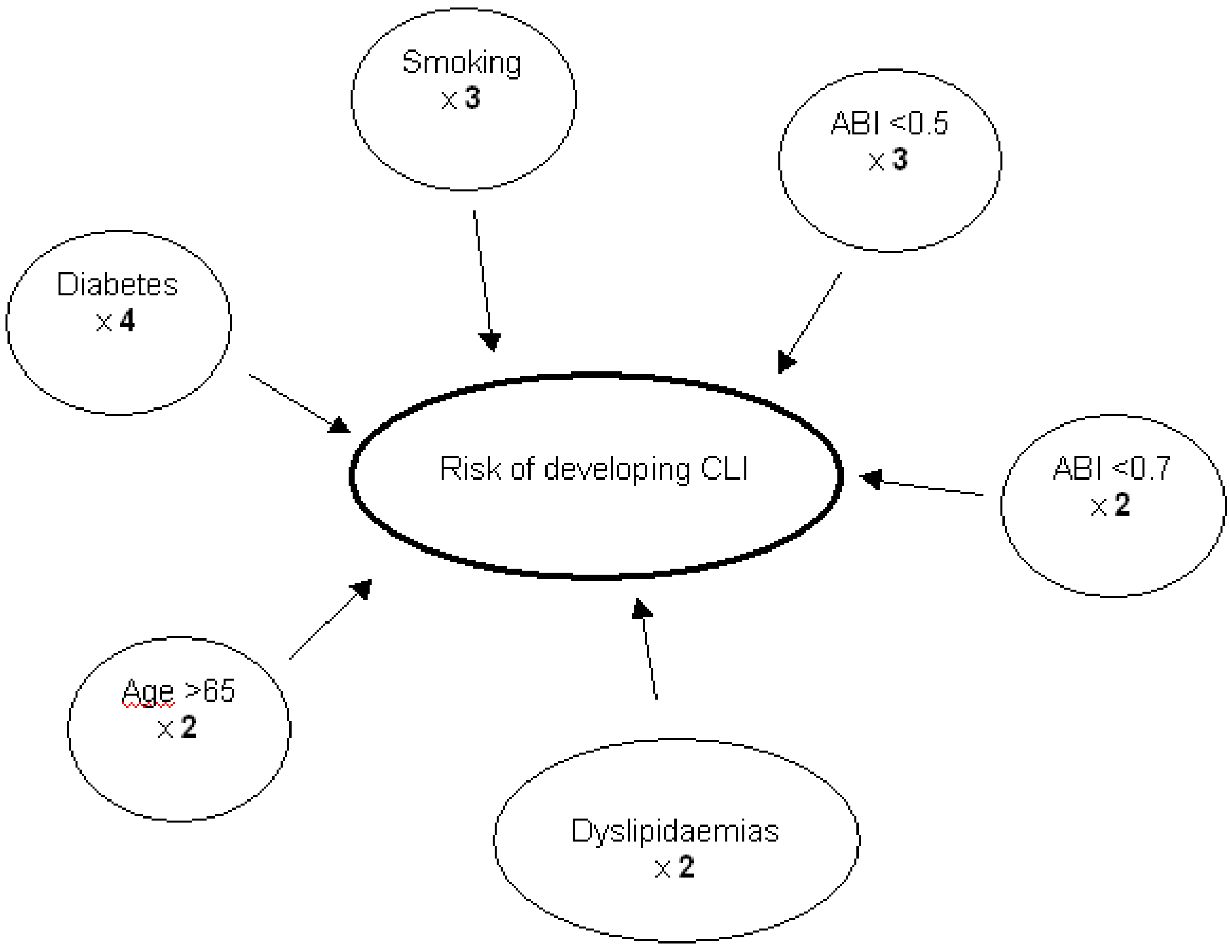


Figure 2. The influence of different risk factors on the progression of PAD with subsequent development of CLI (Dormandy et al. 1999e).

6.2.4 Fate of a patient with critical limb ischaemia

One and five-year mortality rates of patients with CLI are reported to be 20-25% and 40-70%, respectively (Dormandy et al. 1999b; ICAI 1997; Wolfe and Wyatt 1997; Wolfe 1986). Within 10 years, 95% of CLI-patients representing with tissue loss and 80% of patients with rest pain were dead (Dormandy et al. 1999b). The main causes of death for CLI patients are cardiovascular (Luther 2003).

The reported primary amputation rates among patients with CLI vary between 10% and 40% (Dormandy et al. 1999b). The European working group on CLI estimated that one year after the diagnosis of CLI, 55% of all patients would be walking on two legs, 20% would be dead and 25% alive and have undergone amputation (Second European Consensus Document 1992). The same document recommends revascularization for the treatment of CLI if there is more than a 25% chance of patient survival and limb salvage for one year.

Most patients with CLI nowadays undergo some form of revascularisation of the leg. Thus, it is difficult to describe the natural history of a critically ischaemic limb. Patients not suitable for active treatment are the only cases providing unmanipulated outcome data, and do not represent the whole CLI group. A large proportion of these are patients whose general condition is so poor, or whose atherosclerosis is so widespread, that arterial reconstruction is not feasible (Heikkinen 2003). Lepäntalo and Mätzke (1996) studied the outcome of CLI in 105 patients with 136 critically ischaemic legs treated conservatively. One-year mortality was 54%, and at one year 46% of the critically ischaemic legs had been amputated while 28% of the patients were alive with the nonamputated leg (Lepantalo and Matzke 1996). In a study of 37 nonreconstructed patients with CLI, Jivegård and his colleagues reported 35% to be alive at one year with the nonamputated leg (Jivegard et al. 1995). The available data from conservative treatment series of CLI patients thus gives amputation-free survival rates in the range 28-35% at one year (Jivegard et al. 1995, Lepantalo and Matzke 1996) and 27% at two years (Klomp et al. 1999).

Dormandy and co-workers (Dormandy et al. 1999b) have summarised the outcome data of different surgical and conservative series of CLI patients as shown in Figure 3**.**

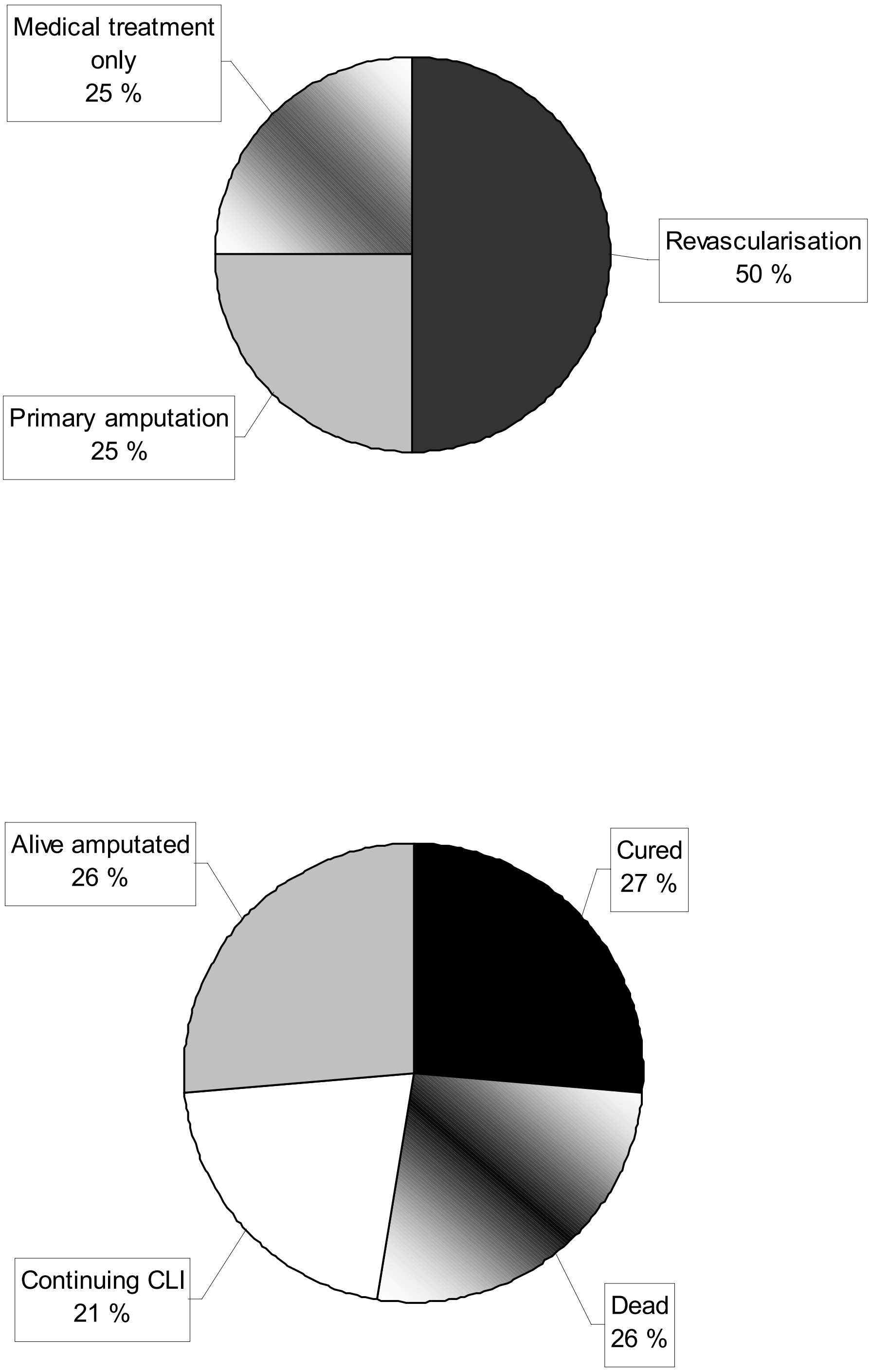


Figure 3. Initial treatment of patients with CLI and their status one year later according to Dormandy and colleagues (Dormandy et al. 1999b).

The fate of the limb is dependent on the degree of CLI. In the study by Bloor (Bloor 1961) the risk for limb loss was 29% in patients with rest pain and almost 100% in patients with ischaemic lesions. In a more recent review the risk for limb loss within a year in patients with rest pain and tissue loss was estimated to be 70% and 95% respectively (Wolfe and Wyatt 1997). The authors concluded that future reports should indeed identify these two groups separately, as the dominant difference between outcome studies is the proportion of subcritical patients (with rest pain, not always with a low ankle pressure) in the study rather than better surgical or radiological techniques. Progression of the atherothrombotic disease also results in a high incidence of CLI in the contralateral limb. Within 3-5 years 30-50% of those surviving may develop contralateral CLI symptoms (Luther 1997).

Because randomized prospective studies comparing long-term survival of patients after revascularisation or major amputation are not possible, comparisons have to be retrospective. These suggest a similar survival in patients undergoing either major amputation or revascularisation (Dormandy et al. 1999b). Some studies have shown shorter survival for patients undergoing amputation than for those with a salvaged leg: Luther (Luther 1994) reported 1- and 5- year survival rates of 55% and 20% respectively after major amputation and 83% and 45% respectively after reconstruction, but the patients were not matched. Ouriel and colleagues (1988) found that survival was similar in amputees with less severe co-existing medical illness, but amputees with severe medical illnesses had a significantly worse perioperative mortality (16% vs 6% respectively) and 3-year survival (29% vs 76% respectively) than those patients undergoing surgical reconstruction (Ouriel et al. 1988). Whether this difference in survival rates is due to the positive influence of reconstruction or only an expression of the varying severity of the disease and selection of patients remains an unanswered question.

6.3 Lower limb amputation incidence rates

6.3.1 Crude incidence data

In the Nordic countries the incidence of major lower limb amputations due to vascular causes was 320/million inhabitants in 1979 in Malmöhus county, Sweden (Liedberg and Persson 1983). The incidence of vascular amputations was 342 and 274/million inhabitants in Varberg, Sweden, during the periods 1985-88 and 1989-92 respectively (Karlstrom and Bergqvist 1997) and 160/million inhabitants in the catchment area of the Karolinska Hospital (Wahlberg et al. 1994) during the period 1989-92. The incidence of all major lower limb amputations was 409/million inhabitants during the period 1986-87 in the county of Viborg in Denmark and 309/million during the period 1989-90 (Lindholt et al. 1994). Ebskov et al (1994) reported major lower limb amputation incidences of 345 and 250/million inhabitants in Denmark in 1983 and 1990 respectively.

Tunis et al reported (1991) vascular lower limb amputation incidences of 280-320/million inhabitants of Maryland, USA in 1979-1985, whereas Hallett and co-workers (1997) reported amputation incidences of 367 and 190/million inhabitants of another community (Olmsted County, Minnesota) in the USA between 1973-77 and 1988-92 respectively. In a study by Feinglass and colleagues (Feinglass et al. 1999), the amputation rate was 250/million inhabitants in 1996 in the USA. Jones (1990) found the incidence of all amputations in three Australian states to be 236/million in 1984 (Jones 1990) and Mattes and colleagues (1997) reported the incidence of vascular major lower limb amputation to be 103/million inhabitants in Western Australia during the period 1980-92. Rommers and colleagues (1997) reported the incidence of all lower limb amputations to be 180-200 during the period 1982-1993 in the Netherlands. Pell and his co-workers (1994) reported a vascular age-adjusted major amputation incidence of 142/million in 1990 in Scotland.

The incidence of all lower limb amputations in Southern Finland was 325-281, 220, 274 and 282/million inhabitants in 1984-85, 1989, 1992 and 1995 respectively (Alaranta et al. 1995; Laaperi et al. 1993; Pohjolainen and Alaranta 1988; Pohjolainen and Alaranta 1999). In a nation-wide study in Finland, the overall incidence of major lower limb amputations was 216 / million inhabitants per year in 1993-94 (Luther et al. 2000), varying from 140 to

330/million inhabitants between different central hospital catchment areas. In the Pirkanmaa region of Finland, the incidence of major lower limb amputations varied from 102 to 248/million inhabitants between the different subregions during the period 1990-1999 (Heikkinen et al. 2002). Probably one of the lowest rates of incidence of major lower limb amputation currently in Finland is found in the region of Vaasa central hospital, where it was 108/million inhabitants during the period 1995-99 (Luther 2002). Previous rates for this region were 317, 276 and 274/million inhabitants during the periods 1980-84, 1985-89 and 1980-91 respectively (Luther 1994; Luther et al. 1996).

In a multicenter study in Europe, North America and East Asia there were marked differences in the overall incidence of all major amputations(Group TG 2000). However, similar distributions by age and sex were demonstrated (Table 8). The highest rates for men and women were in the Navaho area. The lowest rates for major amputation were in the Japanese and Spanish centres. There were marked differences between European centres. Rates in Madrid (Spain), Vicenza (Italy) and Leicester (UK) were substantially lower than those in the north of England in Leeds, Middlesborough and Newcastle. In the Navaho population, a very high prevalence of diabetes was likely to be the explanation for the high amputation rates. Differences between other populations did not seem to be related to the prevalence of diabetes; it seemed likely that differences in the prevalence of peripheral vascular disease are important. Other factors, such as cultural and medical care differences, including access to vascular surgery services, may also be important, but require further investigation (Group TG 2000).

There are difficulties in comparing amputation rates in different studies. Inconsistencies between published studies may relate to the inclusion or exclusion of all major amputations performed for any reason (including other than vascular causes), inclusion or exclusion of people with diabetes in the overall rates, of first-ever, or all, amputations and differences in the level of amputations. In addition, age-specific rates tend not to be presented, making comparison between populations with different age structures difficult. Finally, different studies often use different data sources to identify amputations. It is therefore possible that differences exist in the level of ascertainment of amputations between studies (Group TG 2000)

Table 4. Age-adjusted incidence* of all major amputations in men and women

Centre	Men	Women
Leeds, UK	199	102
Leicester, UK	56	43
Madrid, Spain	28	5
Middlesborough, UK	198	84
Montgomery, USA	192	170
Navaho area, USA	439	320
Newacastle, UK	163	88
Ilan, Taiwan	92	83
Tochigi, Japan	38	12
Vicenza, Italy	69	70

*Incidence per million inhabitants per year in a standard European population according to the Global Lower Extremity Amputation Study Group (Group TG 2000)

6.3.2 The changes in amputation incidence and vascular reconstruction policy

It was noted in the 1980s that the frequency of lower limb amputations was increasing (Liedberg and Persson 1983; Luther 1994; Pohjolainen and Alaranta 1988; Pohjolainen and Alaranta 1999) and was predicted to increase even more in susbequent years with the increase in life expectancy and size of the elderly population (Liedberg and Persson 1983, Pohjolainen and Alaranta 1988, Pohjolainen and Alaranta 1999). The incidence was predicted to increase 50% within the next 20-30 years as shown in Figure 4. (Pohjolainen 1991; Pohjolainen and Alaranta 1988).

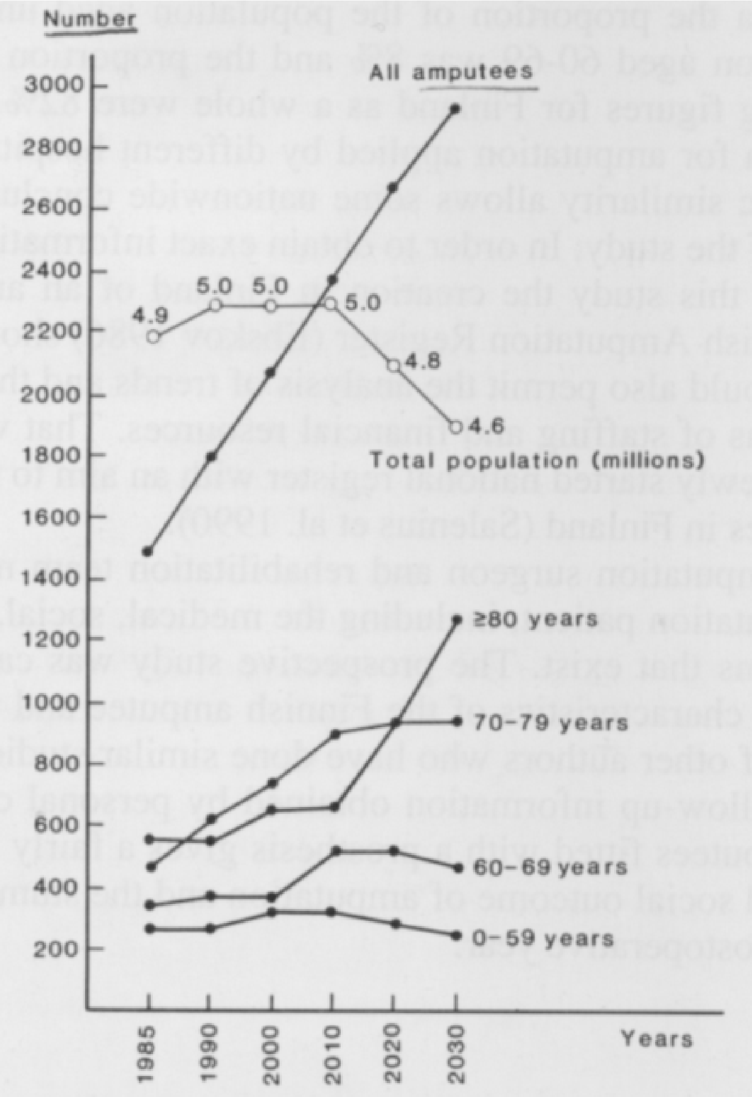


Figure 4. Future trend in the number of amputees (total and by age-group) in Finland estimated on the basis of age-related incidences in Southern Finland 1984-1985 by Pohjolainen 1991.

Currently there is an ongoing controversy, often fuelled by unverified retrospective audit data from large and changing populations (Mattes et al. 1997; Tunis et al. 1991), as to whether there has been a significant reduction in amputations as a result of increasing revascularization procedures in patients with CLI. Institutional reports have shown excellent clinical patient outcome after arterial reconstruction (Tables 5 and 6), but these reports may be misleading in the evaluation of the impact of treatment in the population, as the analysis is skewed by selection bias in referral centres (Luther et al. 1996).

Tunis and colleagues (1991) found that from 1979 to 1989 the annual rate of PTA rose from 10 to 240/million inhabitants in Maryland, USA. The annual rate of peripheral bypass surgery also rose substantially, from 320 to 650/million inhabitants. Despite this, the annual rate of amputation remained stable at about 300/million inhabitants. In this study, however, inclusion criteria were sparse, and the majority of patients treated with revascularisation were claudicants.

A quite recent study of a fixed population in Varberg, Sweden, over 8 years strongly suggests that a decrease in the primary amputation rate (from 42% to 27% in the treatment of limb-threatening ischaemia), associated with a corresponding increase in revascularisations, resulted in an overall decrease in the total amputation rate from 61% to 47% (Karlstrom and Bergqvist 1997). The incidence of vascular amputations was 342 and 274/million inhabitants in Varberg during the periods 1985-88 and 1989-92 respectively (Karlstrom and Bergqvist 1997).

A decline in the major amputation rate has also been reported in a population-based study made in Denmark; from 345/million in 1983 to 250/million in 1990 (Ebskov et al. 1994). This decline coincided with an increase in vascular surgical activity of up to 100%, including a marked rise in the rate of femorodistal reconstruction. Similar results were obtained in another population-based study in Denmark (Eickhoff 1993): the number of lower limb amputations in Denmark for peripheral occlusive arterial disease decreased during the period of increasing vascular surgical activity from 1609 in 1983 to 1181 in 1990.

Activity within one District Health Authority in England has been compared for the periods 1983 to 1987 and 1988 to 1991. There was an 11-fold increase in surgical reconstructions and a 13-fold increase in endovascular procedures. This was accompanied by a 32% decrease in the annual rate of major amputations from 480 to 320/million inhabitants (Gutteridge et al. 1994).

A study from a defined community in the USA reported that major amputation rates decreased by 50% between 1973-77 and 1988-92 from 367/million inhabitants during the first study period to 190/million inhabitants during the second (Hallett et al. 1997). This coincided with a significant increase in vascular surgery and balloon angioplasty.

In a careful longitudinal study of a well-defined and reasonably stable population in Finland from 1970 to 1991, Luther (Luther 1994) showed a 2.5-fold increase in major amputations for ischaemia from 120 in 1970 to 300/million inhabitants in 1981. The increase in numbers of reconstructions for CLI by 100% from 1980 onwards was associated with a reduction in amputation rate of 60% from 1983 to 1991 (being 120/million inhabitants in 1991), despite a significantly ageing population.

Finally, a nation-wide two-year analysis from Finland (Luther et al. 2000) showed an inverse correlation between the incidence of infrapopliteal surgical reconstructions and that of BK amputations in different hospital regions

6.4 Vascular surgery – impact on amputations

Two main open vascular surgical options are available in the treatment of patients with CLI: a vein or artifical conduit can be used to bypass the diseased vessel or, alternatively, stenosing or occluding plaques can be surgically removed – thrombendarterectomy (Lundberg 2005). The extensive vascular disease in CLI generally precludes more limited interventions and is why a bypass procedure is by far the most common surgical operation performed (Lundberg 2005). Advances in surgical technique have greatly increased the number of vascular reconstructions done. The majority of patients with CLI have multisegmental disease with occlusions longer than 10 cm (Bradbury 2003; Salas and Bolia 2003), and an increasing proportion are diabetics whose arterial disease primarily affects the infrapopliteal arteries (Da Silva et al. 1996). Reconstructions for CLI originate below the inguinal ligament in 65-83% of patients (Salenius et al. 1993; The Vascular Surgical Society of Great Britain and Ireland 1995), and in all legs in need of infrainguinal reconstructions the majority have arterial occlusions necessitating infrapopliteal reconstructions (Gibbons and Eiopoulos 1995; Leather et al. 1988; Shearman et al. 2000).

It was shown in a nation-wide study by Luther and colleagues (2000) that increasing the number of infrapopliteal surgical reconstructions for CLI results in a reduction in below-knee-(BK-)amputation. In infrapopliteal reconstructions, autologous vein should always be used when possible due to higher graft patency (Shearman et al. 2000). The autologous long saphenous vein can be used in-situ or reversed with apparently good results (Akbari et al. 2000; Harris et al. 1993; Pomposelli et al. 1995; Sayers et al. 1998). The merit of the reversed method is that both proximal and distal anastamoses can be performed synchronously, reducing operation time, whereas the in-situ technique allows the smaller distal end of the vein to be anastamosed to the smaller run-off artery (Shearman et al. 2000). Over the last decades, several centres have put a great deal of effort into infrapopliteal bypass surgery (IPBS) for leg salvage in CLI (Tables 5 and 6). This increasing reconstruction activity has also been supported by studies showing that the patient’s quality of life is reduced after an amputation (Albers et al. 1992; Pell et al. 1993). In the surgical series of distal reconstructions, major amputation rates ranging from 2% to 34% at 1 year and 12% to 36% at 2 years have been reported (Tables 5 and 6).

Some amputations have been prevented by combining long bypass surgery with microvascular free flap transfer. In addition to anecdotal reports, only four series with life-table analysis on leg salvage are available (Czerny et al. 2004; Moran et al. 2002; Tukiainen et al. 2000; Vermassen and van Landuyt 2000).

Table 5. Outcome of reconstructions for CLI to crural arteries.

					Leg salvage (%)					Survival (%)				
	Legs	DM (%)	FIV (%)	ABI	1m	1y	2y	3y	5y	1m	1y	2y	3y	5y
Leather et al. 1988	1038[1]	-	-	-	-	-	-	-	-	93	-	-	-	-
Hickey et al. 1991	239	24	-	-	-	-	-	-	-	93	81	-	62	60
Anderson et al. 1992	96 (ATA)[2] 65 (ATP)[2] 67 (AP)[2]	-	-	-	95 97 88	90 80 78	-	85 78 74	-	-	-	-	-	-
Synn et al. 1992	53	53	6	CLI[5]	-	81	81	-	-	92	-	-	-	-
Bergamini et al. 1994	77 (AP)[2]	56	52	0.32	96	76	73	-	-		82	77	69	51
Darling et al. 1995	732 (AP)[2]	-	-	-	96	96	-	-	93	96	-	-	-	-
Abou-Zamzam et al. 1996	159	69	52	0.41	-	86	86	-	-	-	60	60	60	-
Luther & Lepäntalo 1997b	209	47	61	-	-	81[4]	-	76[4]	71[4]	-	-	-	-	-
Eslami et al. 1997	130	59	51	0.54	97	-	-	-	79	-	-	-	-	55
Sayers et al. 1998	635	36	-	-	-	81	73	-	-	-	84	74	-	-
Biancari et al. 1999	77	45	58	0.32	94	80	76	76	-	92	83	82	76	-
Van Damme et al. 2003	90[3]	43	57	-	-	-	-	-	89	-	-	-	-	67

DM = diabetes mellitus. FIV = Fontaine IV disease. ABI = ankle brachial index (mean). ATA = arteria tibialis anterior. ATP = arteria tibialis posterior. AP = arteria peronealis.
[1] 88% CLI.
[2] *in situ* vein.
[3] includes four legs with claudication.
[4] prosthetic grafts excluded
[5] stated, that pressure measurements fullfilled CLI criteria, but ABI not given

Table 6. Outcome of reconstructions for CLI to pedal arteries.

					Leg salvage (%)					Survival (%)				
	Legs	DM (%)	FIV (%)	ABI	1m	1y	2y	3y	5y	1m	1y	2y	3y	5y
Anderson et al. 1992	23[1]	-	-	-	92	74	-	68	-	-	-	-	-	-
Tannenbaum et al. 1992	56[2]	100	100	-	100	98	-	98	-	98	95	-	83	-
Bergamini et al. 1994	175	74	78	0.35	93	77	74	-	-	-	82	77	69	51
Gloviczki et al. 1994	100	-	-	0.55	95	85	-	79	-	100	90	-	83	-
Darling et al. 1995	238[1]	-	-	-	95	94	-	-	86	94	-	-	-	-
Pomposelli et al. 1995	384	95	90	-	98	94	-	92	87	98	90	-	75	57
Shah et al. 1995	106	78	-	-	98	93	-	93	93	97	-	-	-	47
Abou-Zamzam et al. 1996	46	70	100	0.43	-	70	70	70	-	98	84	75	69	-
Luther and Lepäntalo 1997a	109	74	84	0.43	87	66	64	-	-	96	80	69	54	-
Biancari et al. 1999	165	70	84	0.46	88	66	66	60	-	95	75	69	55	-
Akbari et al. 2000	962[3]	83	89		-	-	-	-	87	-	-	-	-	58
Biancari et al. 2000	66[4]	79	89	CLI[5]	97	88	88	-	-	94	-	72	-	-

DM = diabetes mellitus. FIV = Fontaine IV disease. ABI = ankle brachial index (mean).
[1] *in situ* vein
[2] diabetes with infection
[3] includes 58 legs with claudication and 18 asymptomatic legs with failing grafts
[4] includes 18 crural grafts
[5] stated, that pressure measurements fullfilled CLI criteria, but ABI not given

6.5 Endovascular procedures – impact on amputations

Since the first description in 1964 (Dotter and Judkins 1964), percutaneous transluminal angioplasty (PTA) has played an increasingly important role in the treatment of peripheral vascular disease (Nasr et al. 2002; Pell et al. 1994). The role of PTA in treating CLI patients has become an issue of increasing interest, but also a source of controversy (Bradbury et al. 2002; Bradbury and Ruckley 1996).

According to the TASC document only 5-35% of patients with CLI would be candidates for angioplasty if the selection is made by ”favourable anatomy” (TASC 2000), which in general terms means only stenotic lesions or short occlusions. There is a lot of evidence that PTA is highly effective in treating patients with peripheral arterial disease involving the aorto-iliac system (Parsons et al. 1998). However, in the treatment of CLI, the effectiveness of PTA remains controversial when arterial segments below the inguinal ligament are involved, with one-year patency ranging from 12% to 88% (Parsons et al. 1998; TASC 2000; Varty et al. 1998). In addition, the majority of patients with CLI have multisegmental disease with occlusions longer than 10 cm. Yet it has been suggested that the technique of intentional subintimal recanalisation / angioplasty, first described by Bolia and his associates, would be the endovascular solution to treat them (Bolia et al. 1989; Bolia et al. 1990; London et al. 1994; Reekers and Bolia 1998).

The results of PTA in treating critical limb ischaemia during the 1980s and 1990s were mainly fairly poor (Bradbury 2003). Limb salvage rates for the patients treated varied from 50% at 5 months (Zarins et al. 1980) to 56% at one year (Matsi 1995).

Recent papers reporting on the results of infrainguinal angioplasty as treatment for CLI patients show excellent limb salvage rates of up to 91% at 5 years (Boyer et al. 2000; Dorros et al. 2001; Faglia et al. 2002; Jamsen et al. 2002; Nasr et al. 2002) (Table 7). Interestingly, many studies reported high limb salvage and clinical improvement rates (72-89% in 2-3 years), regardless of the patency rates (Boyer et al. 2000; Lofberg et al. 1996; London et al. 1995).

Table 7. Outcome of infrainguinal angioplasty for CLI.

					Leg salvage (%)					Survival (%)				
	Legs	DM (%)	FIV (%)	ABI	1m	1y	2y	3y	5y	1m	1y	2y	3y	5y
Zarins et al. 1980	6	-	100	0.2	-	50	-	-	-	-	-	-	-	-
London et al. 1995	54	49	63	0.43[1]	-	-	89	-	-	-	-	76	-	-
Matsi et al. 1995	117	77	76	-	77	56	49	49	-	91	70	-	-	-
Löfberg et al. 1996	86	-	98	0.3	-	-	-	72	-	-	-	-	-	-
Parsons et al. 1998	257	63	-	-	-	-	-	-	-	-	-	-	-	-
Varty et al. 1998	84	-	-	-	82	76	-	-	-	94	78	-	-	-
Boyer et al. 2000	49[2]	73	59	34[3]	100	87	87	87[2]	-	100	92	81	75	-
Dorros et al. 2001	284[4]	62	43	CLI[7]	-	-	-	-	91[5]	-	90	86	78	56
Löfberg et al. 2001	92	43	75	0.3	-	-	-	-	86[6]	96	-	-	-	51
Faglia et al. 2002	221	100	100	0.53	-	95	-	-	-	-	95	-	-	-
Jamsen et al. 2002	116	76	80	CLI[7]	-	-	-	65	60	-	-	-	41	26
Matsagas et al. 2003	50	50	-	0.4	-	98	-	-	-	96	73	67	59	-
Molloy et al. 2003	133	39	69	-	-	88	-	-	-	-	76	-	-	-

DM = diabetes mellitus. FIV = Fontaine IV disease. ABI = ankle brachial index (mean).
[1] 56% of patients with ankle pressure > 50 mmHg
[2] at three years only nine limbs at risk
[3] mean ankle pressure in nondiabetics and toe pressure in diabetics
[4] not on intention-to-treat basis
[5] 18 limbs with bypass included
[6] limb salvage for combined endovascular and vascular interventions
[7]. stated, that pressure measurements fullfilled CLI criteria, but ABI not given

There are even centres with a policy of treating the majority of CLI patients with (subintimal) angioplasty, based on their understanding that the results of subintimal angioplasty could be superior to surgery (Molloy et al. 2003; Varty et al. 1998). There have been, however, criticisms brought against the reports from the Leicester group (Bradbury 2003), as other studies have shown poor long-term patency rates with subintimal angioplasty (Laxdal et al. 2003; Tisi et al. 2002; Yilmaz et al. 2003). It has been pointed out that it remains difficult to explain why the Leicester group´s experience is so uniquely favourable both in terms of the number of patients who appear suitable for the technique, the immediate technical success rate and the complication rate and medium-term durability (Bradbury 2003). While exceptional interventional skill is probably a factor, it seems likely that a significant proportion of the Leicester patients had subcritical limb ischaemia (Wolfe and Wyatt 1997) as opposed to true CLI (Bradbury 2003). Yet, very recent data from other centres confirms the good results of the Leicester group in treating CLI with subintimal angioplasty (Reekers 2002; Spinosa et al. 2004).

6.5.1 Comparison of endovascular treatment with vascular surgery in the treatment of CLI

There are two nation-wide studies comparing the results of surgery versus PTA in treating CLI patients (Luther et al. 2000; Zdanowski et al. 1998). Zdanowski and co-workers reported (1998) from Sweden that the outcome of these two treatment modalities was similar regarding amputation, whereas, in contrast, the study by Luther et al. (2000) in Finland favoured infrapopliteal bypass operations. Both studies were population-based and with groups that were by no means comparable.

The Cochrane Database of systematic reviews has accepted two prospective randomised trials comparing bypass operations and PTA among CLI patients (Holm et al. 1991; Wilson et al. 1989). Pooling both trials showed no overall significant difference in amputation rates between the surgery and PTA groups (OR 1.48, 95% CI 0.79, 2.77). These findings must, however, be viewed with caution, as only iliaco-popliteal lesions were included in these two studies. Patients with multilevel disease, or those requiring tibial or pedal artery bypass, would not be eligible for angioplasty, so the trials include only a subset of patients with CLI. Randomisation of CLI-patients to either of these two treatment modalities can, indeed, be difficult (Holm et al. 1991). In this particular study, although it may seem historical from the perspectives of today´s practices, only 5% of patients were eligible for either treatment modality. Thus no generalisation is possible, as 95% of patients were exluded. Proper randomised controlled trials require a large number of patients with easily definable inclusion criteria. The major problem related to lower limb occlusive changes is the multitude of anatomic varieties and therefore poor comparability, which is illustrated by the attempts to classify lower extremity arterial disease (TASC 2000).

As has been stated in some reports (Boyer et al. 2000; Doubilet and Abrams 1984; Lofberg et al. 2001; Matsagas et al. 2003), failure after attempted endovascular revascularisation rarely compromises a subsequent surgical bypass option, which may support the use of endovascular techniques in cases of uncertainty.

To date, there is no evidence-based data (level I) to support systematically either modality as a first-line treatment for CLI (Bradbury 2003). The same patients may receive entirely different treatment depending on which hospital they attend and which consultant they see (Bradbury et al. 2002). Results from the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-trial from the United Kingdom will hopefully give us more information on this matter (Bradbury et al. 2002).

6.6 Management of the diabetic foot – impact on amputations

The incidence of diabetes mellitus is increasing worldwide. The incidence of type I diabetes in Finland was 36.5 /1000 000 in the year 2000, and is predicted to be 50 /100 000 by the year 2010 (Onkamo et al. 1999; Steck and Rewers 2004). Accordingly, a rising trend in the prevalence of type II diabetes has also been reported in Finland (Laakso et al. 1991). The statistics of the Social Insurance Institution of Finland showed that, at the end of 1990 and 2002, 100 023 and 145 731 diabetic patients respectively were entitled to reimbursements of their medical expenses, thus presenting a 53% increase in 12 years. Both increased incidence and decreased mortality among diabetic subjects have contributed to the increased trend in the prevalence of diabetes (Laakso et al. 1991).

Ischaemic foot ulceration in the diabetic patient is a source of great physical and emotional stress to the patient and represents a significant burden for the health care system and costs to the payer (Gibbons et al. 1993; International Consensus on the Diabetic Foot 1999; Kellicut et al. 2003). Approximately 15% of patients with diabetes will have a foot ulcer (Gibbons and Eiopoulos 1995), and 85% of all diabetes-related lower extremity amputations are preceded by a foot ulcer (International Consensus on the Diabetic Foot 1999). The most important factors related to the development of foot ulcers are peripheral neuropathy, minor foot trauma and foot deformities. The severity of lower extremity arteriosclerosis, on the other hand, is the main independent risk factor for major amputation (Faglia et al. 1998; Lepantalo et al. 2000). Diabetic patients account for 40-70% of all lower extremity amputations (International Consensus on the Diabetic Foot 1999; Mätzke 2004). The prevention, assessment, and treatment of diabetic foot ulcers and CLI has, fortunately, improved in recent years.

6.6.1 Multidisciplinary foot care team approach

The implementation of a multidisciplinary team approach in the prevention and treatment of diabetic foot ulcers has been reported to be an effective means of preventing amputations in the diabetic patient (Edmonds et al. 1986; Gibbons et al. 1993; Holstein et al. 2000; Larsson et al. 1995; Morris et al. 1998; van Houtum et al. 2004). Using a multidisciplinary team, which preferably consists of an internist, podiatrist, orthopaedic or plastic surgeon and vascular surgeon, rehabilitation physician, orthopaedic shoemaker, and diabetes specialist nurse (van Houtum et al. 2004), a reduction in amputations as high as 50-85% has been described (Larsson et al. 1995; van Houtum et al. 2004). In a population-based study by Larsson et al (1995), the incidence of diabetic major amputations decreased by 78% from 160 / million inhabitants in 1982 to 36 / million inhabitants in 1993 in the Lund University Hospital catchment area in Sweden. In 1983, a multidisciplinary diabetic foot team was established in the area. However, a considerable decrease was also noted in amputations for vascular disease without diabetes. There is one published nation-wide analysis of the incidence of diabetes-related lower limb amputations, and it shows a 36% decrease in amputations in men and a 38% decrease in women with diabetes in the Netherlands over the period 1991-2000 (van Houtum et al. 2004). The impact of vascular surgery or a diabetic-foot team as a whole on these figures was not truly analysed. In addition, all lower limb amputations were included in the analysis. Likewise, in a nation-wide study from Finland, the number of first amputations at any level in diabetic people decreased from 767 to 385 per 100 000 diabetics from 1989 to 2002 (Winell 2005).

6.6.2 Diabetes and the outcome of infrainguinal reconstructions for CLI

The operative management of CLI has undergone an evolution over the last 3 decades. Diabetic people, in contrast to those without diabetes, often have a pattern of atherosclerotic vascular disease which spares the superficial femoral and popliteal arteries. The crural vessels, on the other hand, show occlusions of variable extent, while the pedal vessels remain patent (Da Silva et al. 1996). Despite decreased survival among diabetics (AhChong et al. 2004; Luther and Lepantalo 1996; Luther and Lepantalo 1997b; Wolfle et al. 2003), there is strong evidence that bypass grafting to the leg is worthwhile (Akbari et al. 2000; Pomposelli et al. 1990; Pomposelli et al. 1995; Sayers et al. 1994; Sayers et al. 1993; Wolfle et al. 2003). Holstein and collegues (2000) reported that the incidence of major amputations in patients with diabetes decreased from 272/million inhabitants in 1981 to 69 / million inhabitants in 1995 in Copenhagen, Denmark. At the same time, infrapopliteal arterial bypass was introduced for the treatment of CLI, and in diabetic patients the number of these bypasses increased from 0 to 130/million inhabitants (Holstein et al. 2000).

Patency rates and limb salvage rates after infrainguinal revascularization in diabetic and non-diabetic patients have been reported to be equal (AhChong et al. 2004, Akbari et al. 2000, Luther and Lepantalo 1996, Pomposelli et al. 1990; Pomposelli et al. 1995, Wolfle et al. 2003). A combination of female gender and diabetes has been shown to have a negative influence on patency and leg salvage (Luther and Lepantalo 1997b).

In a nation-wide analysis of diabetes as a risk factor for postoperative mortality and morbidity after surgery for CLI in Finland during the period 1991-1999, diabetes was found to be an independent risk factor for postoperative BK amputation (Virkkunen et al. 2004). The acute graft occlusion rate was equal for diabetics and nondiabetics, emphasising the independent role of diabetes in increasing the risk of amputation (Virkkunen et al. 2004). In cases in which the graft was patent at 30 days, significantly more diabetics than nondiabetics underwent amputation, supporting the suggestion that in diabetics reconstruction is often performed too late, and that diabetics more commonly must undergo amputation due to major tissue loss, despite successful revascularisation (Virkkunen et al. 2004).

In general, published papers do not reveal what the exact role of a multidisciplinary foot-care team has been in decreasing amputation figures.

6.7 Conservative treatment – impact on amputations

Conservative treatment for CLI is recommended only in patients with unreconstructable arterial changes, when there are contraindications to reconstruction or as a temporary treatment while planning for reconstruction (Luther 1997). Series assessing the outcome in patients unsuitable for revascularisation, or with failed bypass attempts, report major amputation rates ranging between 32-50% at six months of follow-up (Klomp et al. 1999; Norgren et al. 1990; The U.K. Severe Limb Ischaemia Study Group 1991). Only a few studies have a follow-up longer than six months. In a study by Lepäntalo and Mätzke, the amputation rate at 12 months was 46% (Lepantalo and Matzke 1996). In a study by Jivegård et al, the amputation rate at 18 months was reported to be 54%, as was the major amputation rate at 24 months in a study by Klomp and co-workers (Jivegard et al. 1995; Klomp et al. 1999) (Table 8).

Table 8. Outcome of critical leg ischaemia with conservative treatment.

	N	DM (%)	FU (months)	Mortality (%)	Major amputations (%)
Norgren 1990[1]	53	34	6	15	45
UKSLISG 1991[1]	71	49	6	11	47
Jivegård 1995[2]	26	19	18	30	54
Klomp 1999[2]	60	38	24	68	54
Lepäntalo & Mätzke 1996	105	50	12	54	46

N = number of patients. DM = diabetes mellitus. FU = Follow-up. UKSLIG = UK Severe Leg Ischaemia Study Goup.
[1] Randomised studies with prostanoid treatment.
[2] Randomised studies with epidural stimulation as treatment.

The impact of pharmacological therapies on the outcome of CLI has proved to be limited. Prostanoids (intravenous Iloprost or prostaglandin E1) seem to be a treatment with some effect on rest pain and healing of ischaemic ulcers for a short period of time (ICAI 1997; Norgren et al. 1990; The U.K. Severe Limb Ischaemia Study Group 1991). In two randomised and placebo-controlled studies, an oral prostacyclin analogue (Iloprost) showed no clear benefit in patients with CLI (The Oral Iloprost in severe Leg Ischaemia Study Group 2000). The TransAtlantic Inter-Society Consensus (TASC) for the management of peripheral arterial disease recommends the use of prostanoids in patients who have a critically ischaemic yet still viable limb in which revascularisation procedures are impossible, carry a poor chance of success or have previously failed, and particularly when the alternative is amputation (TASC 2000).

For patients with CLI, electrical spinal cord stimulation (SCS) has been advocated for the treatment of ischaemic pain and the prevention of amputation. However, there are only two carefully planned prospective randomised controlled trials testing this hypothesis (Jivegard et al. 1995; Klomp et al. 1999). In a rather small study, Jivegård and colleagues (1995) reported SCS to provide long-term pain relief, but limb salvage at 18 months was not significantly improved by SCS. In a study by Klomp and colleagues (1999), 120 patients with CLI, but not suitable for reconstruction, were randomly assigned either to SCS plus the best medical treatment or to the best medical treatment alone. SCS did not prevent amputation in the study. Thus, SCS should be used only when all possibilities for revascularisation have been excluded and probably only in selected cases (Klomp and Steyerberg 2005).

It was previously assumed that all patients with severe ischaemia would at some stage require major amputation if not treated surgically or radiologically. Although data concerning the natural history of the conservative treatment of CLI is sparse (Second European Consensus Document 1992), it is known that a proportion of these limbs do not progress to amputation. In some instances conservative or medical treatment may be sufficient. There appears to be a less severely affected group of CLI patients with so-called subcritical ischaemia (tissues intact and ankle pressure of >40 mmHg) in whom limb loss does not appear to be inevitable, and pharmacotherapy or conservative treatment may buy sufficient time for the crisis to pass (Wolfe and Wyatt 1997), especially if revascularisation appears to have risks. On the other hand, there is no evidence that the use of some mode of conservative treatment could improve limb salvage for the high risk group of CLI patients with tissue loss and /or ankle pressure < 40 mmHg (Wolfe and Wyatt 1997).

6.8 Amputation in the treatment of CLI

In some vascular patients amputation is the only option to relieve pain and remove a non-healing infected limb. If an ischaemic and infected leg or gas- or septic gangrene causes an immediate threat to a patients´s survival, an immediate major amputation is mandatory (TASC 2000). Unreconstructable arterial disease is generally due to the progressive nature of the underlying atherosclerotic occlusive condition. There is still a group of vascular patients, though a diminishing one, with limb vasculature unsuitable for a revascularisation procedure or whose leg condition (because of widespread gangrene or vast infection) makes the leg unsalvageable (TASC 2000). It was estimated by Shearman et al in 2000, that in 10% of patients it will be deemed technically impossible to revascularise the limb, or the procedure will fail (Shearman et al. 2000). Critical leg ischaemia of bed-ridden patients should be treated by amputation at a sufficiently high level to avoid healing problems (Luther 1997). PAD-patients with terminal or near-terminal co-morbidities will not gain any benefit from revascularisation procedures either, as the combination of leg salvage and survival is so poor (Biancari et al. 2000; Humphreys et al. 1995; Johnson et al. 1995). Primary amputation may be the best choice in these patient groups (Johnson et al. 1995, Luther 1997) if amputation is needed (Wolfe and Wyatt 1997).

Secondary amputation is indicated when vascular intervention is no longer possible or when the limb continues to deteriorate despite the presence of a patent reconstruction (TASC 2000). In different series, the proportion of cases in which revascularisation had been attempted prior to amputation varies between 23% and 97 % (Holdsworth 1997; ICAI 1997; Luther 1994; Taylor et al. 1991). The most common indication for secondary amputation is bypass thrombosis, accounting for nearly 50% of such cases (Reifsnyder et al. 1997; Wahlberg et al. 1994). Failure of limb salvage despite patent bypass is the second common indication (Reifsnyder et al. 1997).

Decisions on whether to perform revascularisation or amputation in a given patient are multifactorial and must include an estimate of operative risks, the probability of successful revascularisation, the potential gain from successful revascularisation and the patient´s own wishes. Whatever the decision, all patients with CLI should be seen by a vascular surgeon before amputation is recommended (Lepantalo et al. 2000; Shearman et al. 2000; Wahlberg et al. 1994).

6.9 Fate of an amputee

There is rather limited information on the rehabilitation of patients who have undergone amputation in Finland. Epidemiological trends for lower limb amputees have, however, been studied in Southern Finland in four surveys for the years 1984-1995 (Alaranta et al. 1995; Laaperi et al. 1993; Pohjolainen and Alaranta 1988; Pohjolainen and Alaranta 1999). Trends for amputees in the study area in four previous surveys are shown in Table 9.

Table 9. Trends in the amputees in four previous surveys from Southern Finland.

	1984-1985	1989	1992	1995
Incidence per million inhabitants	325 - 281	220	274	282
BK / AK -ratio	0.54	0.57	0.78	0.95
Mortality - unilateral - 2 mo[1]				
AK	32%	28%	32%	28%
BK	17%	16%	19%	17%
Mortality - all - 1 yr[2]	39%	36%	37%	40%

BK = below-knee amputation. AK = above-knee amputation.
[1] Mortality during the first two postoperative months among unilateral amputees.
[2] Mortality of all amputees during the first postoperative year.

The below-knee amputee walking with a prosthesis expends 25% to 40% more energy than in normal walking. In contrast, the above-knee amputee walking with a prosthesis expends 65% to 100% more energy than normal (Meier 2000). According to the literature, approximately 70% of patients with BK-amputation and 10-30% of patients with AK-amputation will walk with a prosthesis (Krupski 2000). After bilateral amputation, 10-25% of patients with AK- and BK-amputation will walk, but after bilateral AK-amputation, the wheelchair becomes the only practical method of achieving mobility, if mobility can be realistically achieved at all (Meier 2000). Much lower figures for rehabilitation of amputees have also been presented: at a Veterans Affairs hospital in a series of 229 patients with major amputation, 65% of BK-amputees and 80% of AK-amputees were not able to walk after amputation during a 7-year study period in 1994-2001 (Cruz et al. 2003). In a study by Houghton and colleagues in England, 440 vascular amputations during a two-year study period were assessed. Thirtyone percent of the amputees received a prosthesis, 10-15% achieved mobility at home, but only 5% rehabilitated well and became independent of their wheelchair (Houghton et al. 1992).

Generally, two to three times more BK amputees achieve full mobility than AK amputees (Cruz et al. 2003; Dormandy et al. 1999c; Turney et al. 2001). Received wisdom commends a policy of maximizing the ratio of BK- to AK- amputations in patients with end-stage arterial disease. A BK / AK-ratio greater than 1 has been reported in many series (Aulivola et al. 2004; Campbell et al. 1994; Christensen and Klarke 1986; Cruz et al. 2003; Gutteridge et al. 1994; Hallett et al. 1997; Houghton et al. 1992; McWhinnie et al. 1994; Morris et al. 1998; Turney et al. 2001). According to some researchers the BK/AK-ratio should be closer to 2 than 1 (Dormandy et al. 1999c), although the TASC Document is pleased with 1 (TASC 2000). Opposite views have also been taken: McWhinnie and colleagues (McWhinnie et al. 1994) concluded that increasing the proportion of BK-amputations from one-third to two-thirds of lower limb amputations for occlusive arterial disease did not improve effective rehabilitation rates; instead it appears that a patient will derive more rehabilitation potential from a good AK-amputation than a marginal BK-amputation.

Early hospital mortality rates after BK-amputation range in most series from 3% to 14%, whereas the hospital mortality after an AK-amputation ranges from 3% to 35% (Aulivola et al. 2004; Cruz et al. 2003; Houghton et al. 1992; TASC 2000). This is thought to be due to allocating the older and high-risk patients who have little prospect of rehabilitation to the AK-amputee group (Aulivola et al. 2004; Cruz et al. 2003). However, several reports have related operative mortality to a coexisting medical condition such as diabetes and cardiovascular, cerebrovascular and respiratory disease and found no significant correlation (TASC 2000). In two years, mortality rates of 25% to 35% for BK- and 45% for AK-amputees are seen (TASC 2000), and it appears that the mortality for amputations associated with this high-risk group has remained essentially unchanged over the past 30 years (Cruz et al. 2003; Kazmers et al. 2000). After BK-amputation 50% of patients are dead within 5 years, 30% of patients will undergo a contralateral major amputation and 20% will be alive with the contralateral leg intact (Dormandy et al. 1999c). In other words, the survival probabilities at 7.5 years for BK-amputees and AK-amputees are 28% and 20% respectively (Cruz et al. 2003).

7. AIMS OF THE PRESENT STUDY

The main purpose of this study was to evaluate the changing trends in the incidence and outcome of major amputation in two well defined areas as well as the impact of infrainguinal reconstructions and percutaneous transluminal angioplasty (PTA) on the amputation figures for critical leg ischaemia (CLI).

The specific aims of the studies were to assess:

1) The annual incidence of major amputation and amputation trends in the Seinäjoki Central Hospital region **(I)**
2) The annual incidence of major amputation and amputation trends in Southern Finland **(II)**
3) The impact of infrainguinal reconstructions on major amputation incidence figures in a population-based analysis during a long study period **(II)**
4) The relationship between infrapopliteal reconstructions for CLI and major amputation in a nation-wide analysis of the elderly (≥70 years) population **(III)**
5) The outcome of infrainguinal PTA for CLI patients in terms of patency, limb salvage and survival **(IV)**
6) Changes in diabetes-related and non-diabetes-related vascular lower extremity amputations in the city of Helsinki **(V)**

8. MATERIAL AND METHODS

Study I: A retrospective study was undertaken during the period 1997-2000 at the Seinäjoki Central Hospital and Ähtäri District Hospital in the Etelä-Pohjanmaa region, with a catchment area population of about 200 000 (area I). Patients treated in Ähtäri were only accounted for in the amputation incidence figures, and their records were not reviewed. The annual number of amputations was recorded. A total of 169 major lower limb amputations in 156 patients were reviewed. Data relating to the following were analysed: amputee demographics, diagnosis leading to amputation, vascular status of the limb before amputation, amputation level and postoperative morbidity, mortality, prosthesis fitting, ambulation and the state and place of stay of the patient one year after amputation. The follow-up period was one year.

Study II: In a retrospective survey for the year 2000 covering a catchment area of 1.4 million inhabitants, patient data was gathered from hospital records in the eight surgical hospitals in Southern Finland (area II). A total of 215 major lower limb amputations in 174 patients were analysed. Data on the following were analysed: demographic factors, diagnosis, amputation levels, postoperative complications and the state and place of stay of the patient one year after amputation. The follow-up period was one year. Amputation data for the period 1984-1995 in the study area was gathered from earlier reports in the same area, and amputation figures for the period 1990-2001 were also obtained from the National Research and Development Centre for Welfare and Health (Stakes). Comparisons with amputation incidence (admissions during which an amputation was done) between years 1990 to 2000 were made in numbers gathered from Stakes to reassure similar calculation. The relationship between the incidences of infrainguinal (or infrapopliteal) bypass and major amputation was analysed for these years. The annual age-adjusted amputation incidence could be calculated for the period 1990-2001. Although the year 2000 was the actual end-point in this study, amputation figures for 2001 were also included to show the trend in figures.

Study III: A nation-wide, retrospective study for the year 1997 was undertaken analysing data from Stakes on hospital discharges, including demographic, ICD-10 and operative information on the vascular patients. Elderly patients (≥70 years of age) undergoing infrapopliteal bypass surgery or major lower limb amputation for CLI were included in the study. The 21 Finnish central hospital regions were divided into two groups of equal size according to their activity in treating patients aged 80 or over using infrapopliteal reconstructions. Activity was defined by the incidence of infrapopliteal reconstruction among patients aged 80 or over in each region. The ”active group” (group A) consisted of 11 hospital regions with a total of 83 905 people over 80 years of age living in their area. The ”passive group” (group B) consisted of 10 hospital regions with a total of 82 305 people aged 80 or over living in their catchment area that year (Table 10). As the study is nation-wide and each hospital region treats the population living in it’s catchment area, the two groups should be rather similar with regard to risk factors and confounding factors, especially as the allocation of the regions to one or other of the groups had no geographical preponderance. Group A performed 102 infrapopliteal reconstructions on patients aged 80 or over, while group B performed only 7 distal bypasses on such patients. The incidence of amputation was calculated and the association between the numbers of amputations and infrapopliteal reconstructions in the oldest age group was analysed.

Study IV: Data on 221 patients with 230 critically ischaemic limbs treated with consecutive infrainguinal PTAs at Helsinki University Central Hospital between January 2000 and December 2002 were collected and analysed retrospectively. Patient data were gathered from hospital records, the local hospital registry (the HUSVasc Registry) and angiograms. Survival data were also gathered from the Population Register Center.
The indication for PTA, pre- and post procedural toe pressures and ankle-brachial (ABI)-values, demographic data on patients, angiographic data on treated lesions, data on postprocedular complications and clinical status of the leg as well as the patients after the PTA were gathered. The mean-follow-up time at the outpatient clinic was 6.7 months (range 0-40 months). Patients risk factors are shown in Table 11. Patency, limb salvage and survival rates were calculated on an intention-to-treat basis.

Study V: The clinical records of 1094 patients who underwent major lower limb amputations for vascular disease in the city of Helsinki during the 13-year period from 1990 to 2002 were analysed retrospectively. Data concerning patient factors, diagnosis, existence of diabetes and amputation level were recorded. Diabetes was defined according to WHO. The study period was divided into three periods (1990-1994, 1995-1998 and 1999-2002) and results were compared between diabetic and nondiabetic vascular amputees for these periods. To ensure accurate incidence figures during the study period, the total number of major amputations in Helsinki was also cross-checked against figures from the National Research Centre for Welfare and Health (Stakes).

Table 10. Two groups of hospital regions divided according to their activity in performing distal bypass surgery and amputations for CLI in patients 80 or more years of age.

		80 or more years of age				
Regions	Total population (n)	*n*	Population (%)	Infra-popliteal bypasses (*n*)	Amputations (*n*)	BK amputations (*n*)
Active regions						
A1	795 000	16682	2.1	22	48	27
A2	536 000	19315	3.6	21	38	11
A3	165 000	6472	3.9	4	11	8
A4	207 000	6855	3.3	5	12	2
A5	131 000	4835	3.7	7	6	0
A6	178 000	6081	3.4	4	13	2
A7	167 000	7169	4.3	23	8	1
A8	363 000	9154	2.5	7	29	12
A9	90 000	2458	2.7	5	9	0
A10	71 000	1817	2.6	1	0	0
A11	129 000	3067	2.4	3	7	4
TOTAL	2 832 000	83905	3.3*	102	181	67
Passive regions						
P1	257 000	8510	3.3	2	29	11
P2	79 000	2619	3.3	1	5	1
P3	187 000	7032	3.8	1	15	9
P4	259 000	8149	3.1	0	24	7
P5	109 000	4026	3.7	2	18	4
P6	236 000	8770	3.7	1	23	11
P7	69 000	2860	4.1	0	17	9
P8	200 000	7585	3.8	0	29	12
P9	442 000	15613	3.5	0	36	7
P10	444 000	17141	3.9	0	61	11
TOTAL	2 282 000	82305	3.7*	7	257	82

* Median value.

Table 11. Clinical data and risk factors of 221 patients treated with infra-inguinal PTA for CLI.

Condition	Proportion	%
Coronary artery disease	145 / 221	66
Cerebrovascular disease	48 / 221	22
Hypertension	138 / 221	63
Diabetes mellitus	131 / 221	59
Uremia with hemodialysis	27 / 221	12
Any other chronic disease	158 / 221	72
Dyslipidemia with medication	40 / 221	18
BMI > 25	67 / 149*	45*
Current smoking	39 / 201*	19*

* The information was incomplete due to missing data.

Statistical analysis

The statistical analyses were conducted with SPSS (ver 9.0, 11.0, and 12.0.1) statistical software (SPSS Inc, Chicago, Ill., U.S.A.).

The normality of distributions was established with the Kolmogoroff-Smirnoff goodness-of-fit test with the Lilliefors method of significance correction. The Independent Samples T-test was applied for comparisons between two normally distributed groups. When the distributions were skewed, the Mann-Whitney U-test was applied. (**II, V**)

Differences between two groups with respect to discrete quantitative variables were tested with the Mann-Whitney *U*-test (**III**). Associations between categorical variables were analysed with the Chi-Square -test or the Fisher's Exact -test when appropriate (**I, III, V**).

Correlations between discrete quantitative variables were assessed by calculating the Spearman rank correlation coefficient (**II, III**).

Survival analyses were performed using the Kaplan-Meier method and the Cox regression model. Primary patency, secondary patency, limb salvage, patients alive with leg and survival rates were calculated using the Kaplan-Meier method on an intention -to-treat basis. Survival data obtained in the Kaplan-Meier analysis were compared using the log-rank test (univariate analysis). The Cox multiple-regression model was applied to study differences between groups and to adjust for potential confounding factors. Cox regression analyses provided estimates of survival probabilities and risk ratios (RR) of clinically relevant factors for amputation, end of patency and death. The Wald test was applied to calculate p-values for data obtained from the Cox multiple regression analysis. (**IV**)

Differences between groups were considered statistically significant if the p-values were less than 0.05 in a two-tailed test (**I-V**).

9. RESULTS

Study I: The annual incidence of major amputations decreased from 295 / million inhabitants in 1997 to 152 / million inhabitants in 2000. The mean age of the patients was 78.5 years, but highest, at 80.1, in 2000. The reasons for major amputation and their respective percentages of the total were: CLI with or without diabetes (DM), 79%; acute ischaemia, 14%; DM with infection and without knowledge of arterial occlusive disease, 3.8%; trauma, 1.3%; frostbite,1.3%. The average below-knee (BK) / above-knee (AK) amputation ratio was 0.8 during the period 1997-1999 and the ratio was lowest, at 0.67, in 2000.

The 30-day mortality for all amputees was 10%, and the commonest cause of death was acute myocardial infarction. After one year, 55% of the patients were alive. Mortality during the first postoperative year was significantly higher among the AK-amputees than in the BK-amputated group (Table 12, p= 0.004). At the end of one year, 56.5% of the patients with unilateral BK-amputation had received a prosthesis and 92% of them could walk with it. In comparison, only 10.5% of the patients with unilateral AK-amputation had received a prosthesis and all of these were able to walk with it. One year after amputation the BK-amputees were able to live at home more often than the AK-amputees (Table 12, p=0.004).

Table 12. Postoperative place of stay one year after the operation in study areas I and II.

			% of patients		
			BK	AK	p-value
Place of stay	Home	Area I	34.5	12.3	0.004
		Area II	36.1	12.8	0.001
	Chronic hospital / nursing home	Area I	25.5	20.5	0.53
		Area II	8.5	19.6	0.001
	Exitus	Area I	40.0	67.1	0.004
		Area II	38.9	60.8	0.01

BK = below-knee amputation. AK = above-knee amputation.

Study II: In 2000, the incidence of major amputations (including reamputations) was 154 / million inhabitants. At the same time, 135 legs / million inhabitants were lost and 125 patients / million inhabitants underwent amputation. According to data gathered from STAKES, the incidence of admissions during which an amputation was done was 135 / million inhabitants (Figure 5). The below-knee (BK) / above-knee (AK) ratio was 0.76 (Figure 6).

The reasons for major amputation in 2000 are shown in Figure 7. Miscellaneous reasons included burns, rhabdomyolysis, sepsis and cellulitis.

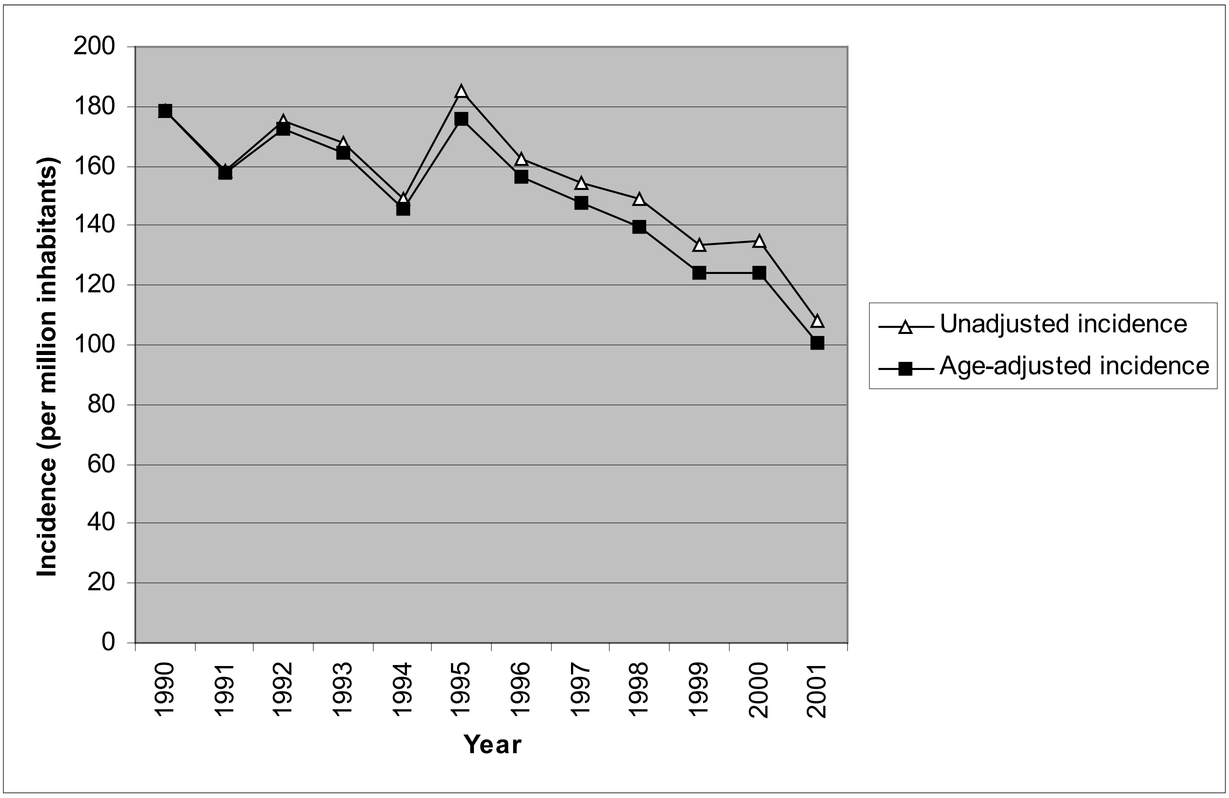


Fig 5. Annual unadjusted and age-adjusted incidence of admissions with major lower limb amputation in Southern Finland 1990-2001.

The mean age of the amputees was 72.4. Patients with AK amputation were significantly older than patients with BK amputations (74.8 versus 69.0, p=0.004). One-week, 30-day and one-year mortality rates for all amputees were 12%, 29% and 52% respectively. Mortality during the first postoperative year was significantly higher among the AK-amputees than in the BK-amputated group (38.9% versus 60.8%, p=0.008**,** Table 12).

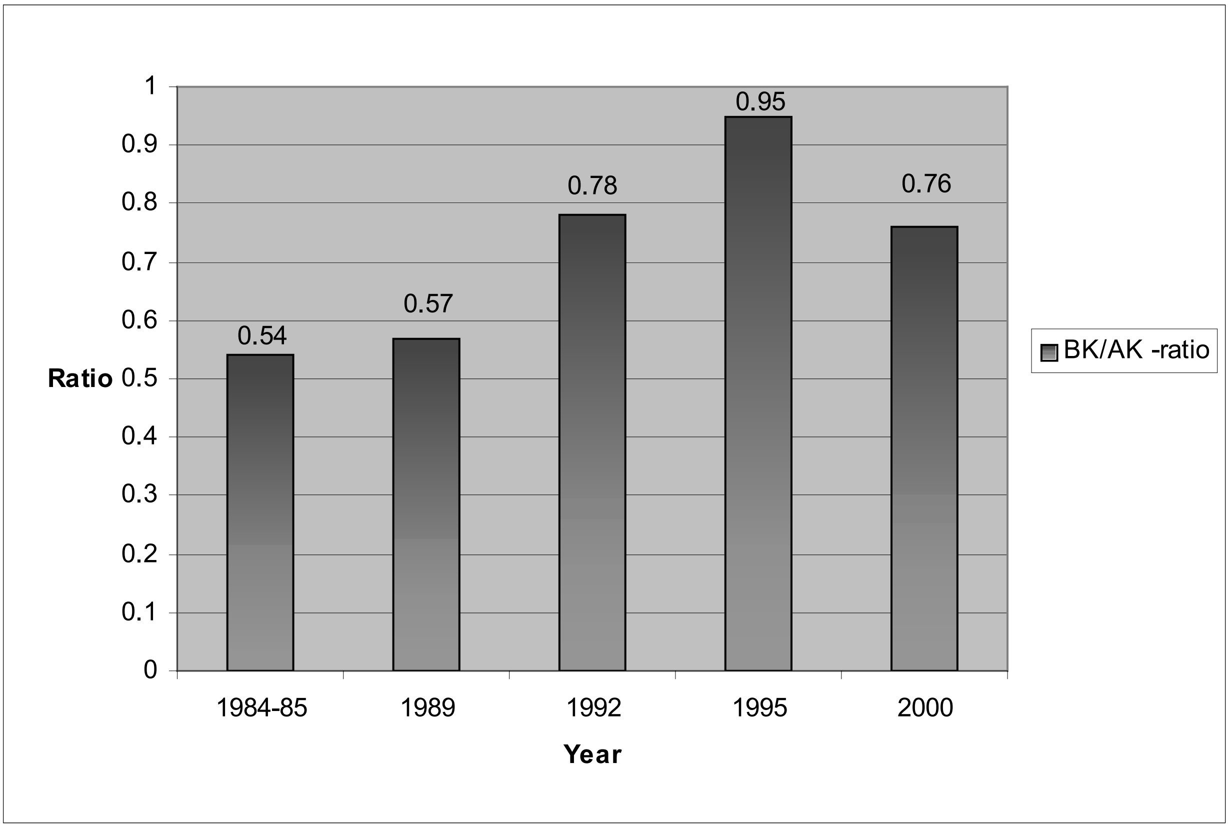


Fig 6. Below-knee / above-knee ratio in Southern Finland. Figures for the years 1984-1995 have been published before. Ratio calculated from lost legs.

One year after amputation the BK-amputees were able to live at home (or in a home-like setting) more often than the AK-amputees (36.1% versus 12.8%, p=0.001). A total of 22% of all patients and 43% of patients alive at one year received a prosthesis. The patients who came from home or a home-like setting received a prosthesis more often than chronic hospital-care patients (42% vs. 2%, p<0.0005). At the end of one year, 68% of patients with unilateral BK amputation who were alive two months after amputation had received a prosthesis, compared to only 19% of the corresponding AK-amputated group. Reliable information on prosthesis usage could not be gathered.

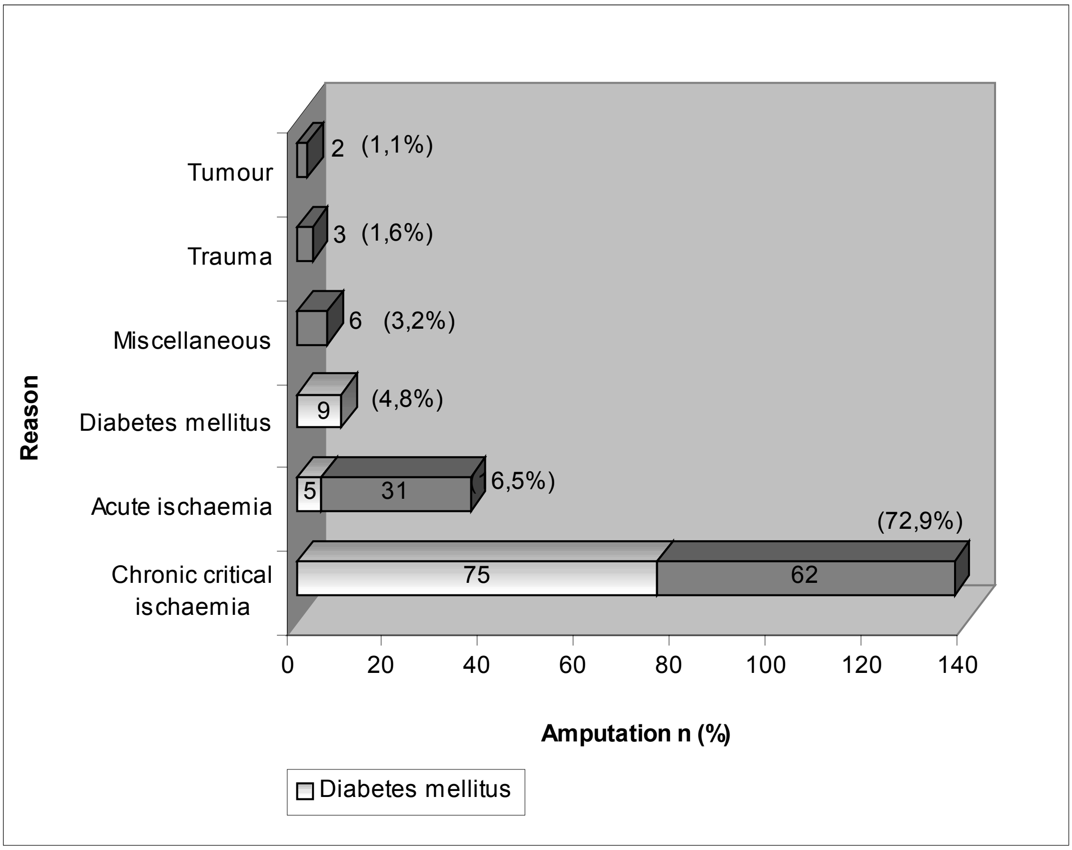


Fig 7. The causes of amputations in 2000 in Southern Finland.

The absolute decrease in the incidence of major amputations from 1984 to 2000 was 41%. Compared with the estimation presented by Pohjolainen and colleagues (Pohjolainen 1991) the decrease was 52% (Figure 8). The decrease in amputation incidence from 1990 to 2000 was 25%, and for age-adjusted amputation the decrease inincidence was 30% (Figure 5). At the same time, the incidence of infrainguinal reconstructions showed an increase of 755% from 1990 to 2000 (Figure 9). The reduction in the number of amputations is clearly continuing: the decrease in the age-adjusted amputation incidence over the period 1990 to 2001 was 44%, and the absolute reduction in incidence from 1984 to 2001 was as high as 52%.

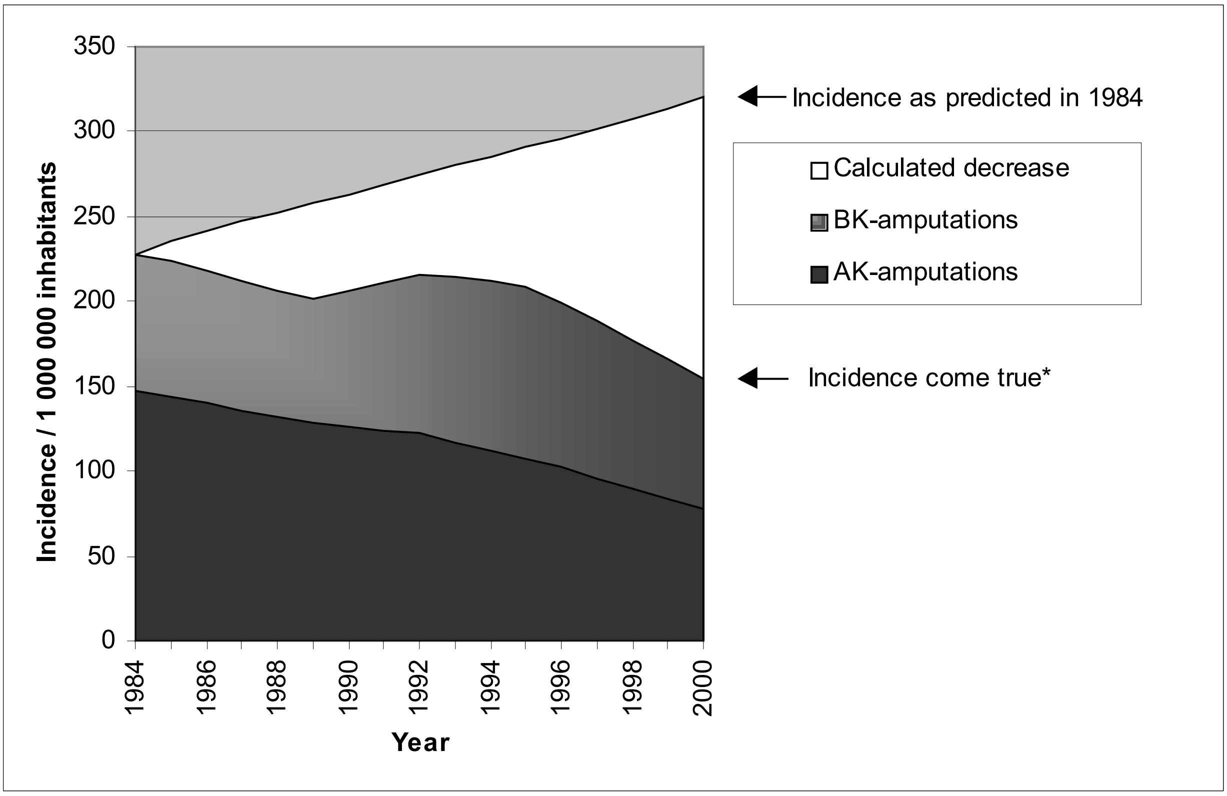


Fig 8. Incidence as predicted in 1984 (Pohjolainen 1991) and the real incidence of amputations in Southern Finland. * Incidence for years 1984, 1985, 1989, 1992 and 1995 have been calculated from figures published before.

For the period 1990-2000 there was a significant inverse correlation both between the incidence of infrainguinal bypass and amputation (r=-0.682, p=0.021) and between the incidence of infrapopliteal bypass and amputation (r=-0.682, p=0.021).

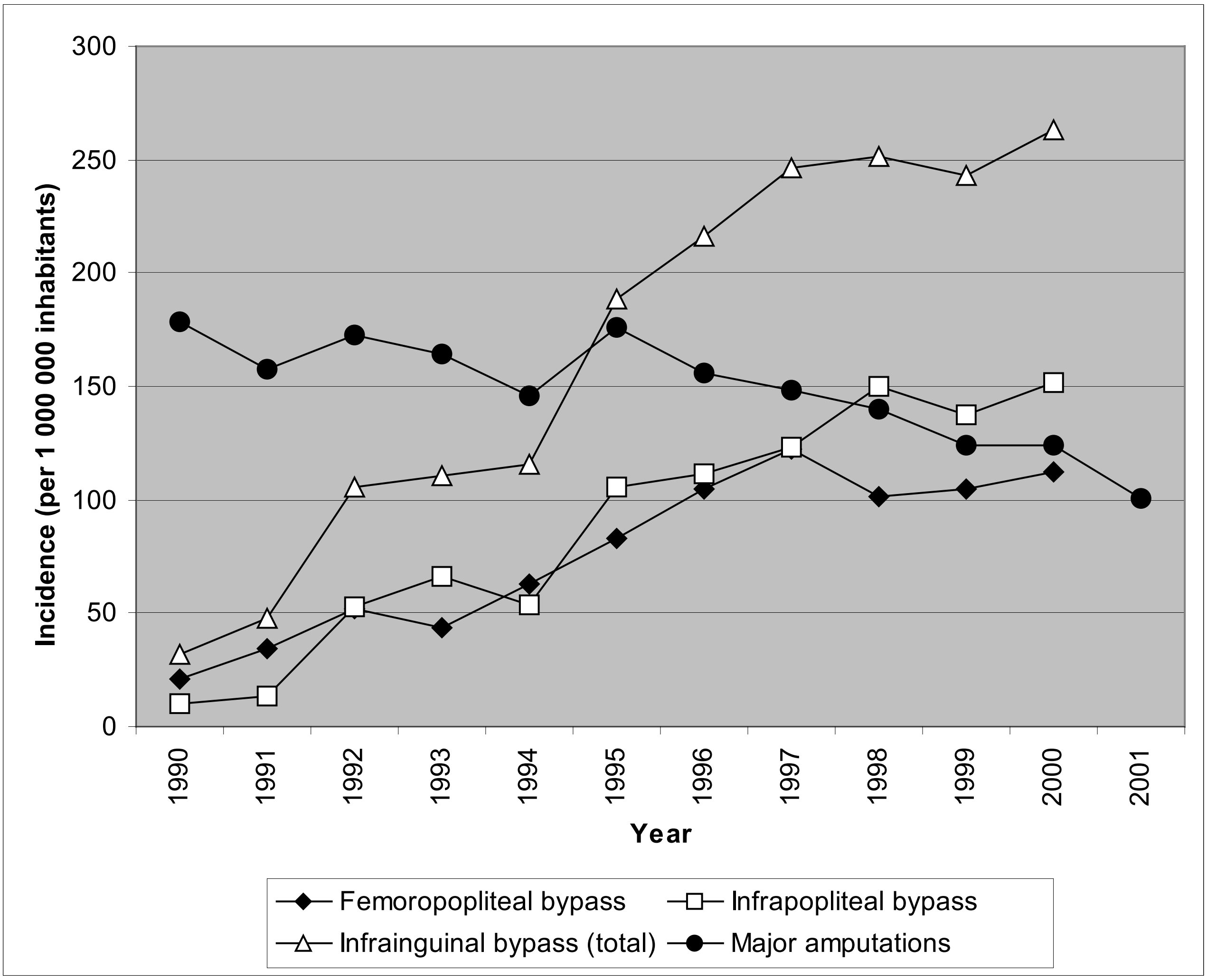


Fig 9. Infrainguinal reconstructions and major amputations in Southern Finland 1990-2001.

Study III: The overall major lower limb amputation incidence in Finland for people ≥80 years of age was 2635/million, and was significantly lower in the active region (group A) than in the passive region (group B) (p=0.016). Similar trends were seen with respect to BK-amputations and in the 70-74 and 65-79 age groups (Figures 10 and 11).

Group A performed significantly more distal bypasses on patients aged 80 or over than group B (*p*<0.0005). Among patients in this age group there was an inverse correlation between the incidence of infrapopliteal reconstruction and the incidence of major lower limb amputation (r= -0.54, *p*=0.012, Table 13). In addition, there was a difference in the incidences of below-knee amputations, even though this correlation was not statistically significant (*p*=0.106). In the age group 70-74, a significant inverse correlation was found between the incidence of distal bypasses and that of BK-amputations (r= -0.63, *p*=0.002, Table 13).

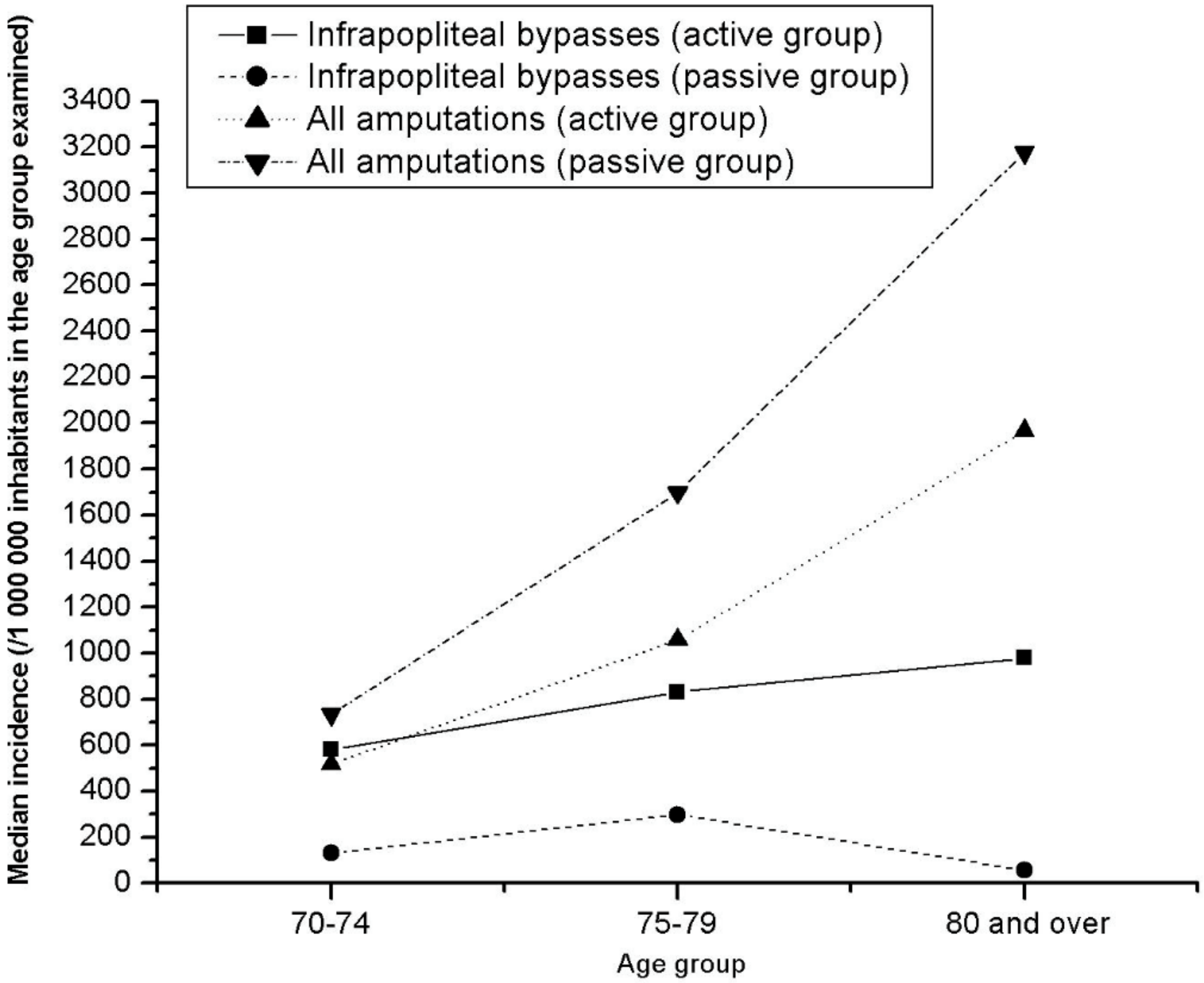


Fig 10. Trend of distal reconstructions and amputations in different age groups.

Table 13. Correlation between the amputation incidence and the incidence of infrapopliteal reconstructions for CLI in different age groups.

Age group	Infrapopliteal reconstructions and all amputations		Infrapopliteal reconstructions and below-knee amputations	
	Spearman's ρ	*p*	Spearman's ρ	*p*
70-74	-0.343	0.118	-0,633**	0.002
75-79	-0.020	0.928	-0.202	0.367
80 and over	-0,535*	0.012	-0.363	0.106

*Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

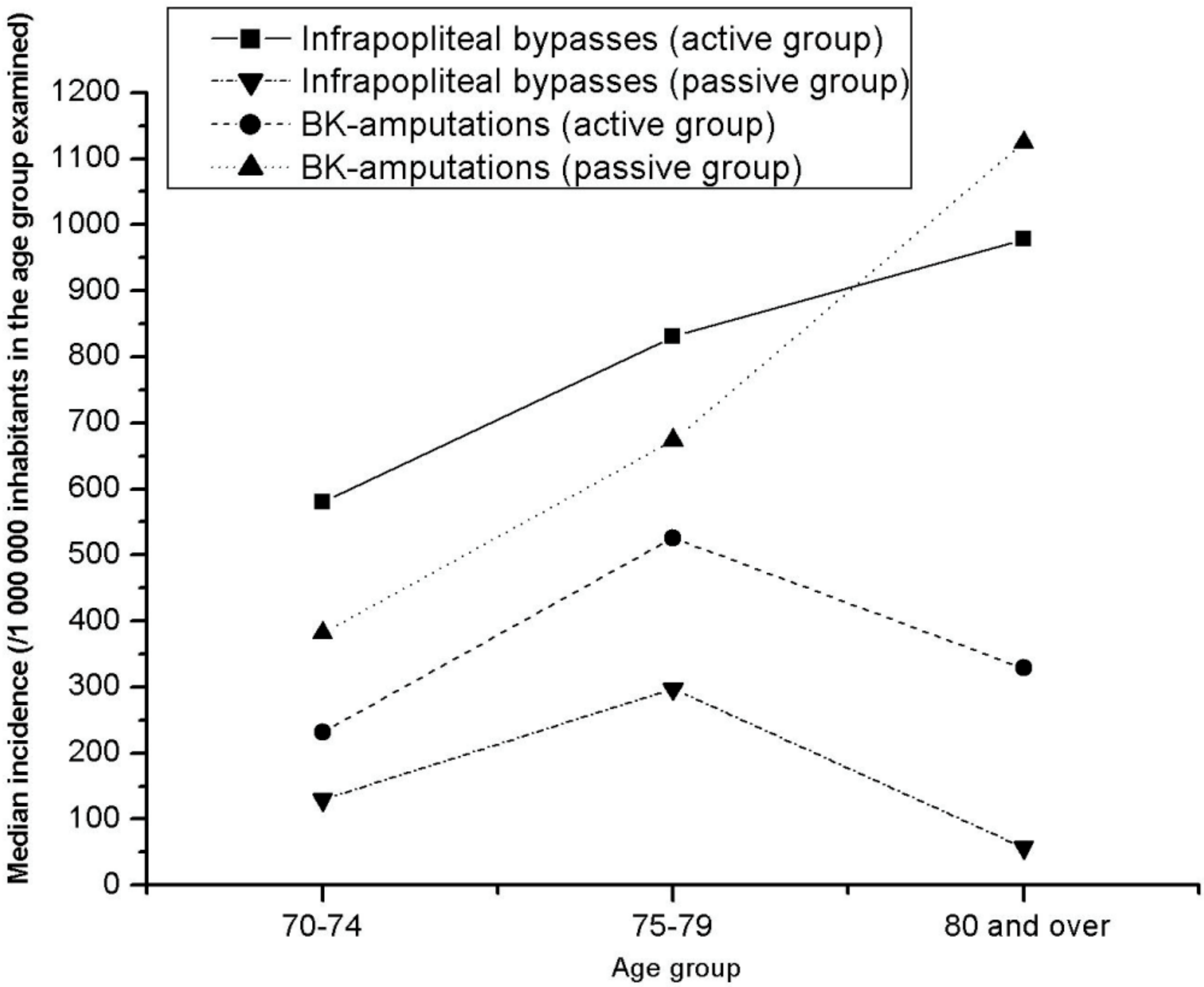


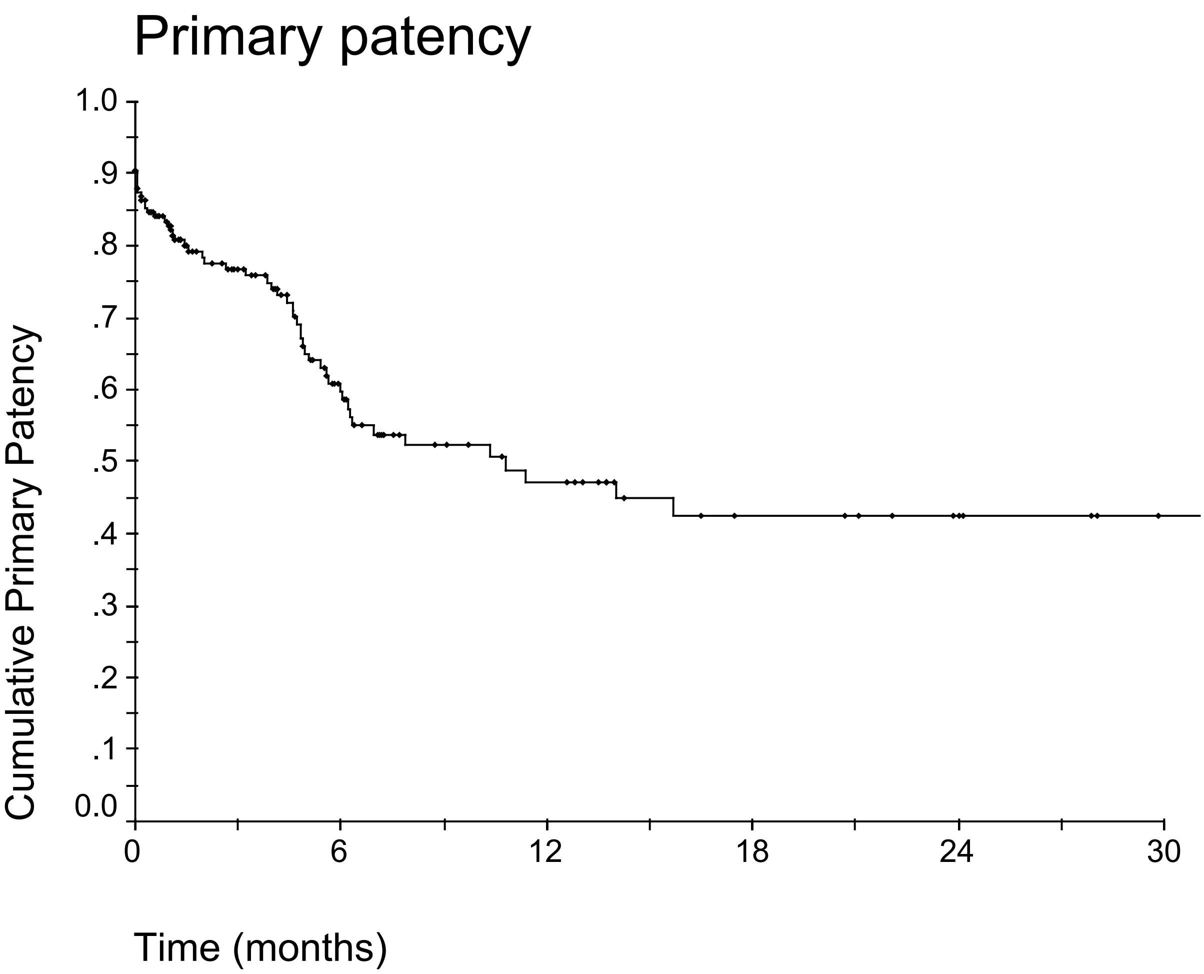
Fig 11. Trend of distal reconstructions and BK-amputations in different age groups.

Study IV: Some form of complication after PTA was encountered in 16 (7%) legs. The most common minor complications were groin hematoma, arteriovenous fistula and thrombosis, all in 3 legs (1,3%). No open surgical procedures were needed for minor complications as they were managed endovascularly when necessary. The major-complication rate was 1%: two patients and limbs (1%) suffered a hemorrhage requiring an emergency operation. The 30-day mortality rate was 4% (n=9).

Patency

The overall primary patency rate at 12 months was 47% (95% CI 37.1-57.3, Figure 12). Uremia with hemodialysis, low toe pressure (≤ 30 mmHg) and age under 70 were found, in a Kaplan-Meier analysis, to be significant risk factors to end patency (Table 14). In the Cox regression analysis, however, only low toe pressure (≤ 30 mmHg) was a significant risk factor to end patency (Table 14).

The secondary patency rate at 12 months was 59% (95% CI 49.3-69.3).



Limbs at risk (n)	86	50	33	27	18	15	14	10	9	5
SEE (%)	3.2	4.4	4.8	5.2	5.4	5.7	5.7	5.7	5.7	5.7

Fig. 12. Primary patency of 230 CLI-limbs treated with infrainguinal PTA in HUCH in 2000-2002 (Kaplan-Meier survival curve). SEE = Standard error of estimate.

Table 14. Kaplan-Meier and Cox regression analysis of factors related to patency in 230 CLI limbs treated with PTA.

Factor	Univariate p-value[1]	Cox-adjusted RR (95% CI)	Cox p-value[2]
Age (< 70 years)	0.0056	1.8 (1.0 - 3.6)	NS (0.07)
Gender (male)	NS (0.085)	1.3 (0.7 - 2.5)	NS (0.47)
DM	NS (0.49)	0.8 (0.4 - 1.6)	NS (0.6)
Uremia with hemodialysis	0.005	1.5 (0.7 - 3.1)	NS (0.25)
Toe pressure (< 30 mmHg)	0.0004	2.6 (1.3 - 5.2)	0.006
Indication (Fontaine IV)	NS (0.97)	0.9 (0.4 - 2.0)	NS (0.77)
Run off (0)	NS (0.25)	1.4 (0.7 - 2.8)	NS (0.57)

RR= risk ratio for the end of the patency. NS = non significant
[1] Kaplan-Meier analysis; overall patency rates compared with log-rank test.
[2] Wald test.

Limb salvage

The overall limb salvage rate was 92% at 12 months (95% CI 88.7-96.1, Figure 13). In a Kaplan-Meier analysis the significant risk factors for amputation were uremia with hemodialysis, poor runoff (0-1), low toe pressure (≤ 30 mmHg) and hemodynamic failure (Table 15). In the Cox regression analysis uremia with hemodialysis, low toe pressure (≤30 mmHg) and hemodynamic failure were found to increase significantly the risk of amputation (Table 15).

Table 15. Kaplan-Meier and Cox regression analysis of factors related to limb-salvage in 230 CLI limbs treated with PTA.

Factor	Univariate p-value[1]	Cox-adjusted RR (95% CI)	Cox p-value[2]
Age (< 70 years)	NS (0.26)	0.6 (0.2 - 1.6)	NS (0.29)
Gender (male)	NS (0.23)	1.8 (0.6 - 5.5)	NS (0.33)
DM	NS (0.24)	1.1 (0.3 - 3.4)	NS (0.89)
Uremia with hemodialysis	0.0005	4.4 (1.4 - 13.4)	0.009
Indication (Fontaine IV)	NS (0.71)	0.7 (0.2 - 2.9)	NS (0.6)
Toe pressure (< 30 mmHg)	0.0029	4.8 (1.5 - 15.4)	0.009
Run off (0)	0.006	2.8 (1.0 - 7.5)	0.04
Hemodynamical failure	0.0008	6.0 (2.1 - 17.5)	0.001

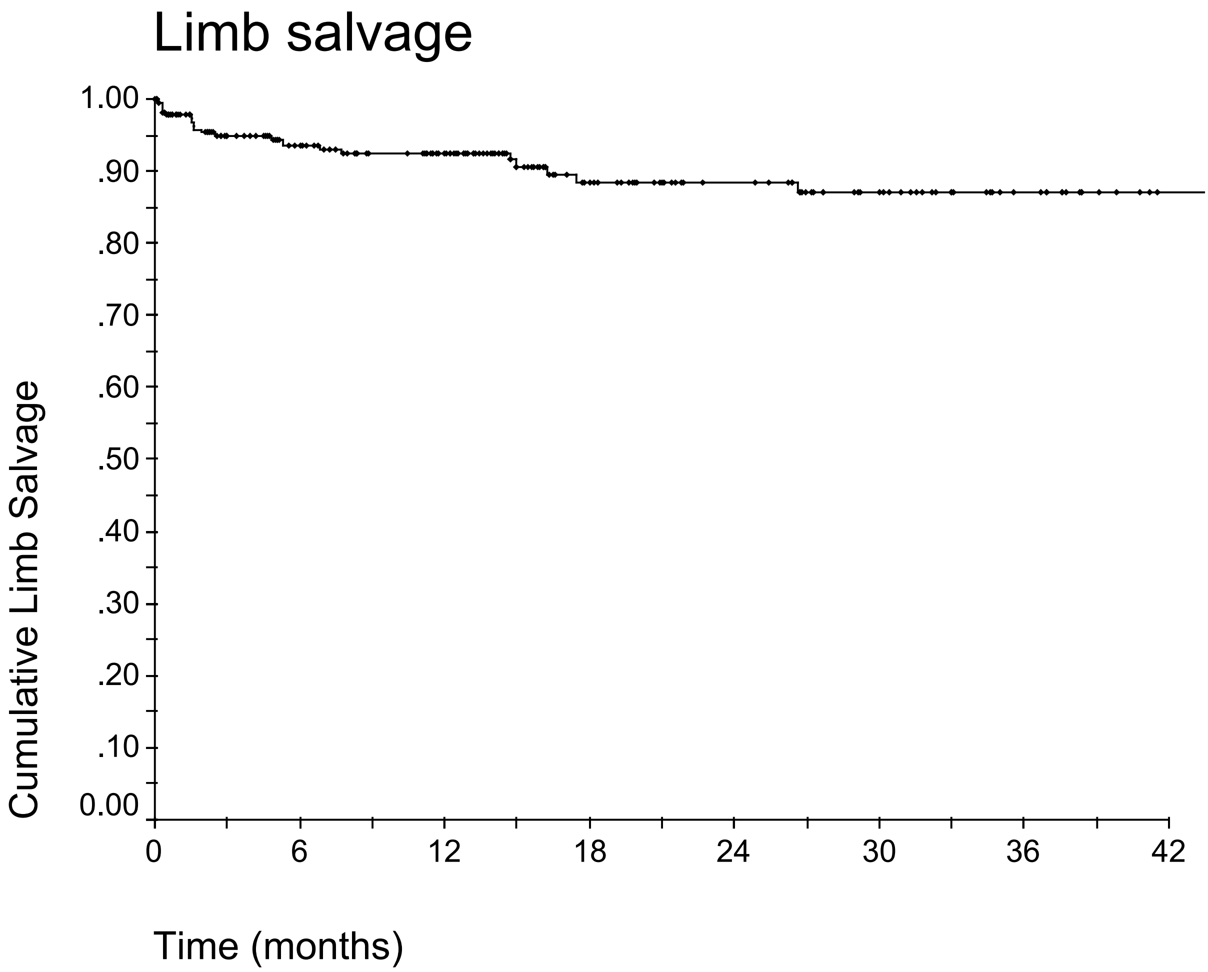
RR= risk ratio for major amputation. NS = non significant.
[1] Kaplan-Meier analysis; overall limb-salvage rates compared with log-rank test.
[2] Wald test.

Survival

The overall cumulative patient survival rates were 76% for one year, 63% for two years and 46% for three years (Figure 14). Uremia with hemodialysis, coronary artery disease, tissue loss as indication for PTA (Fontaine stage IV) and age over 70 years were found to increase significantly the risk of death both in Kaplan-Meier and in the Cox regression analysis (Table 16). In the Kaplan-Meier analysis 66% (95%CI 59.6 – 72.6) of the patients were alive with leg at 12 months.

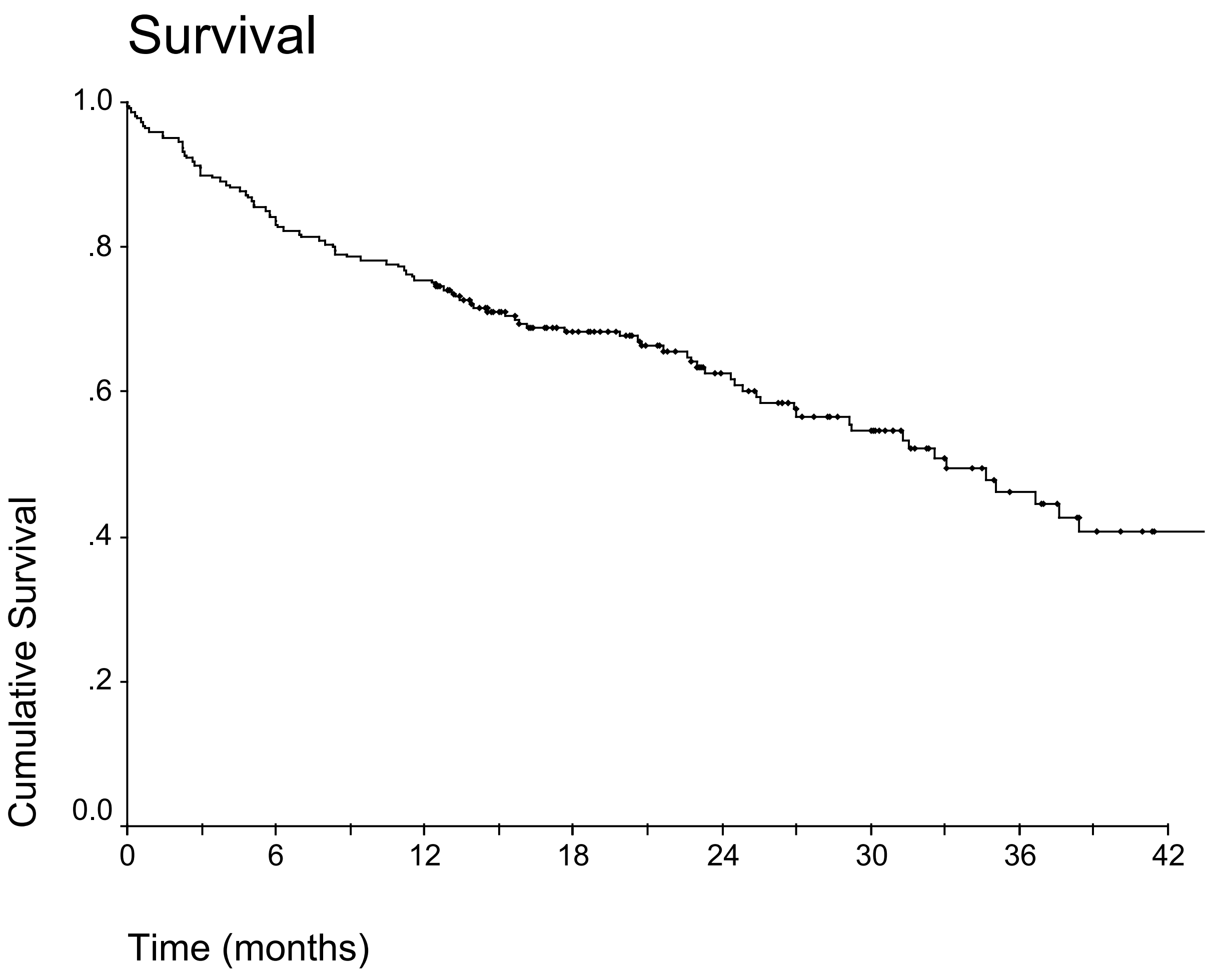
In recent years there has been a large overall increase in endovascular procedures, including infra-inguinal PTAs, at HUCH (Figure 15).

Over the period 1991-2000 there was a significant inverse correlation both between the number of infrainguinal PTA procedures and amputation (r=-0.842, p=0.002) and between the number of infrapopliteal PTA procedures and amputation (r=-0.636, p=0.048).



Limbs at risk (n)	159	125	78	62	42	26	12
SEE (%)	1.7	1.9	2.6	2.6	3.0	3.0	3.0

Fig. 13. Limb salvage of 230 CLI-limbs treated with infrainguinal PTA in HUCH in 2000-2002 (Kaplan-Meier survival curve). SEE = Standard error of estimate.



Patients at risk (n)	184	161	111	77	50	27	14
SEE (%)	2.5	2.9	3.2	3.5	4.0	4.6	5.1

Fig. 14. Survival of 221 CLI-patients treated with infrainguinal PTA in HUCH in 2000-2002 (Kaplan-Meier survival curve). SEE = Standard error of estimate.

Table 16. Kaplan-Meier and Cox regression analysis of factors related to survival in 221 patients with CLI treated with PTA.

Factor	Univariate p-value[1]	Cox-adjusted RR (95% CI)	Cox p-value[2]
Age (> 70 years)	0.0005	2.9 (1.7 - 4.8)	<0.0001
Gender (male)	NS (0.25)	0.9 (0.6 - 1.5)	NS (0.9)
DM	NS (0.18)	1.2 (0.7 - 1.8)	NS (0.5)
Uremia with hemodialysis	0.02	2.3 (1.3 - 4.2)	0.006
Coronary artery disease	0.01	1.7 (1.0 - 2.7)	0.032
Cerebrovascular disease	NS (0.07)	1.4 (0.8 - 2.2)	NS (0.21)
Indication (Fontaine IV)	0.003	3.2 (1.4 - 7.6)	<0.0001
Amputation after PTA	NS (0.33)	0.6 (0.3 - 1.4)	NS (0.23)

RR= risk ratio for major amputation. NS = non significant.
[1] Kaplan-Meier analysis; overall limb-salvage rates compared with log-rank test.
[2] Wald test.

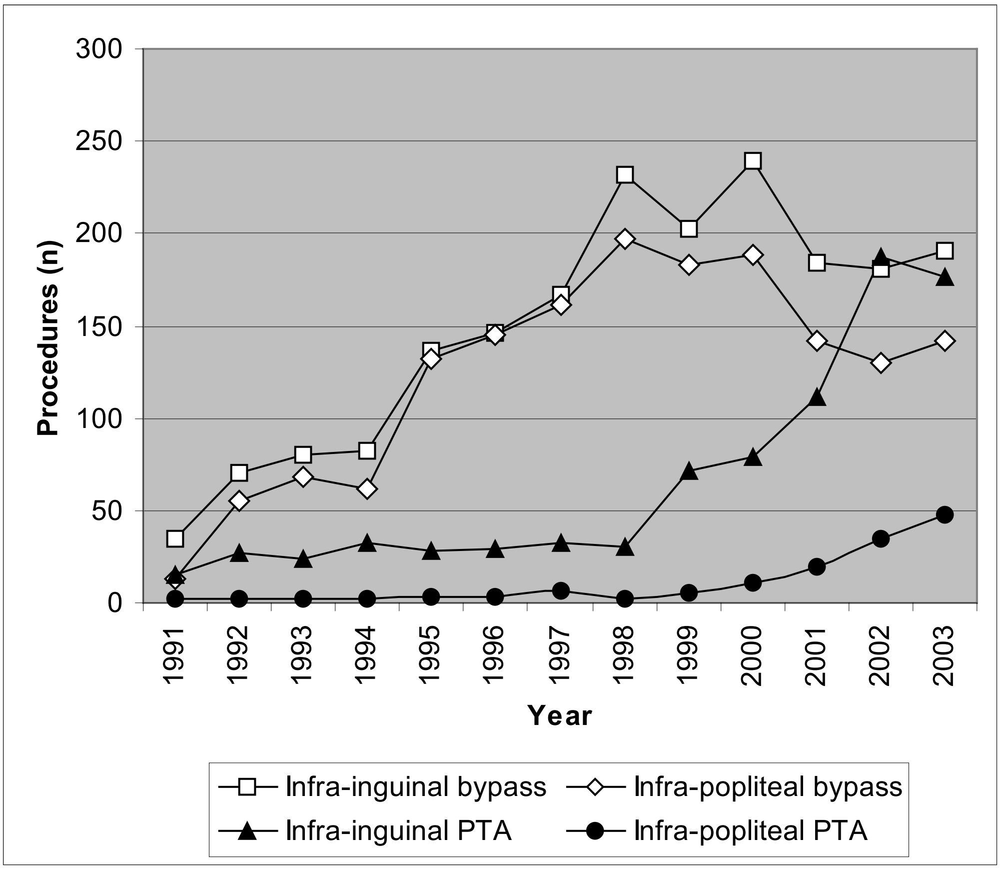


Fig. 15. Infrainguinal vascular procedures for critical leg ischemia in HUCH in 1991-2003.

Study V: From 1990 through 2002, 561 of the total of 1094 patients who underwent major lower limb amputation had diabetes mellitus. Of these, 283 (50,4%) were men. The overall mean age of the diabetics was 72 (range 29-102), significantly lower than that of the non-diabetics (76, range 32-100, p<0.001, Table 17). Male diabetics were younger than the female, the mean ages being 68 (range 31-97) and 76 (29-102) respectively (p<0.001). Among younger diabetic amputees (under 60 years) 74% were male, while 46% of diabetic amputees aged 60 or over were male (p<0.001).

The BK/AK-ratio was significantly lower among nondiabetics (Table 17). The proportion of BK- and AK-amputations among diabetics and nondiabetics over the three time periods are shown in Table 18. Among diabetic amputees aged under 60, 74% had BK-amputation, while 55% of diabetics aged 60 or over had BK-amputation during the study period (Table 18).

Table 17. Comparison of diabetic and nondiabetic vascular amputees.

	DM	**non-DM**	**p**
Age (mean, range)	72.1 (29 - 102)	76.3 (32 - 100)	< 0.001
Gender (% of females, n)	50% (278/561)	56% (297/533)	NS (0.046)
BK/AK -ratio (n)	1.4 (323/238)	0.6 (198/335)	< 0.001

Table 18. Major amputation rates for diabetic and nondiabetic leg ischaemia.

	BK / AK -ratio (n)			
	1990-1994	1995-1998	1999-2002	p-value
Diabetics	1.7 (129 / 74)	1.4 (102 / 73)	1.0 (92 / 91)	0.03
Nondiabetics	0.6 (65 / 114)	0.7 (75 / 113)	0.5 (58 / 108)	NS (0.6)
Diabetics < 60 years of age	5.2 (26 / 5)	2.7 (19 / 7)	1.8 (20 / 11)	NS (0.22)
Nondiabetics < 60 years of age	1.4 (10 / 7)	1.6 (13 / 8)	3.3 (13 / 4)	NS (0.51)
Diabetics > 60 years of age	1.5 (103 / 69)	1.3 (83 / 66)	0.9 (72 / 80)	NS (0.07)
Nondiabetics > 60 years of age	0.5 (55 / 107)	0.6 (62 / 105)	0.4 (45 / 104)	NS (0.43)

The overall incidence of major amputations in diabetics decreased from the first period to the last by 23% (Table 19). At the same time, the incidence of major amputations for vascular disease among non-diabetics decreased from the first period to the last by 40%. By taking into account the prevalence of diabetes in 1990 and 2000 in Finland, diabetes-specific incidence rates could be calculated. According to these calculations, a 33 % fall in major amputations per million individuals with diabetes was observed during the study period.

Table 19. Major amputation rates for diabetic and nondiabetic leg ischaemia.

	Time period			
	1990-1994	1995-1998	1999-2002	p-value
Amputation incidence (DM)*	94.6	84.5	73.2	
Amputation incidence (non-DM)*	89.0	70.7	53.4	
DM in patients < 60 years of age	31 / 48 (65%)	26 / 47 (55%)	31 / 48 (65%)	NS (0.56)
DM in patients > 60 years of age	172 / 334 (52%)	149 / 316 (47%)	152 / 301 (51%)	NS (0.52)

*Mean annual amputation incidence/1 000 000 inhabitants

10 DISCUSSION

10.1 Limitations of the study

Certain limiting factors and selection bias are inherent in most clinical studies, and this is true of our studies too:

Study I:

The first study could be regarded as a survey, as only trends of amputation and amputees were described and the reason for the decrease in amputation incidence was not truly analysed.

Studies II & III:

In these two population-based analyses the incidence of amputation and infrainguinal or infrapopliteal bypass surgery were gathered from the National Research and Development Centre for Welfare and Health (Stakes). These data were collected in a uniform manner from all hospital regions, and systematic errors are therefore unlikely to skew results markedly. Accuracy of registration of data can vary between hospitals and hospital regions in registers operating on a voluntary basis, such as the Finnvasc-registry (Kantonen et al. 1997). In study **III** the pooling of data from many hospital regions should also eliminate the possibility of local factors skewing results. In study **III**, despite collection from a nation-wide register, the numbers of elderly patients undergoing surgery in one year were relatively small, resulting only in trends and not statistically significant differences in some groups.

Study IV:

This study was conducted at an academic referral centre, which may cause some selection bias. The fact that, at this centre, PTA in the treatment of CLI has so far been preferred for only short occlusions and stenotic lesions or in cases when surgery is not possible means that this study population is not comparable with the CLI patients who are operatively managed at the same centre.

Study V:

Patient data for a rather long period of time could be gathered only in the city of Helsinki. To ensure accurate incidence figures during the study period, total major amputation figures in Helsinki were also cross-checked against those from the National Research Centre for Welfare and Health (Stakes). There was some discrepancy between the data gathered from Stakes and that from the hospital records. Average incidence numbers were estimated on the basis of these two information sources.

10.2 General discussion

Currently, there is an ongoing controversy as to whether there has been a significant reduction in amputations as a result of increasing revascularisation procedures in patients with CLI. Institutional reports have shown excellent clinical patient outcome after arterial reconstruction as well as angioplasty, but may be misleading in the evaluation of the impact of treatment in the population, as the analysis is skewed by selection bias in referral centres (Luther et al. 1996). There are, however, some studies which demonstrate the efficacy of revascularisation as a decrease in amputation rates at the populational level (Ebskov et al. 1994; Eickhoff 1993; Gutteridge et al. 1994; Hallett et al. 1997; Karlstrom and Bergqvist 1997; Luther 1994). We conducted two population-based studies **(II, III)** to clarify the association between reconstructions and amputation. In study **II** we analysed a population living in a defined area during a rather long period of time, thus, this study gives long-term amputation data in an era of evolving vascular surgery for limb salvage. In study **III,** data were collected nation-wide for one year. On the basis of our results, we conclude that an increase in vascular infrainguinal reconstructions reduces the number of major lower limb amputations.

The population in most western countries is growing older, with a marked increase in the group of octogenarians and older. The incidence of chronic critical ischaemia shows an increase with increasing age (Dormandy et al. 1999e; Murabito et al. 1997; Reunanen et al. 1982). Several studies have shown a steep increase in amputation rates with increasing age (Group TG 2000; Liedberg and Persson 1983; Luther 1994; Pohjolainen and Alaranta 1988). There are also a number of studies showing that the mobility of the patient is severely restricted by amputation, as few of the elderly amputees can be rehabilitated to walking with a prosthesis (Houghton et al. 1992; McWhinnie et al. 1994; Pohjolainen et al. 1990). This results in high costs to the community, as a large proportion of these patients with restricted ambulation become dependent on care in institutions (Luther 1997). Several authors propose an active reconstruction policy in elderly patients

(Esato et al. 1993; Gouny et al. 1994; Illuminati et al. 2000; Illuminati et al. 1999; Luther and Lepantalo 1997a; Luther and Lepantalo 1997b; Matsubara et al. 2001; McLoughlin et al. 1989; Nehler et al. 1993; O'Mara et al. 1987; Pomposelli et al. 1998; Scher et al. 1986), provided that a successful bypass procedure is likely to improve the quality of life of these patients by maintaining ambulatory function and independent living (Luther 1997).
Yet again, to evaluate the effectiveness of arterial reconstructive treatment in CLI it is essential to evaluate its impact on amputation rates in the population (Luther et al. 1996). With an increasing proportion of patients with critical ischaemia aged 80 or over, it is important to determine if results in this age group justify an active reconstruction policy. On the basis of the results of our study **III,** it is clear that an active approach to distal bypass is associated with a reduced requirement for amputation in this age group especially. Age alone should not be a deterrent to revascularisation for limb salvage.

A nationwide study in Finland showed an inverse correlation between the incidence of infrapopliteal surgical reconstructions and that of below-knee amputations (Luther et al. 2000). Our study group found a similar inverse correlation for the elderly Finnish population **(III)**. In addition, it was found in studies **I**, **II** and **V** that, as the overall incidence of major amputations decreased during the study period, the proportion of AK-amputations rose (BK/AK-ratio decreased). A similar finding was reported in a population-based study in Varberg, Sweden (Karlstrom and Bergqvist 1997) and in Copenhagen, Denmark (Pedersen et al. 1994). Thus, it is apparent that the number of BK-amputations could be altered by infrapopliteal revascularisation and the relative number of AK-amputations inevitably rises. The real index of success in vascular surgery is the proportion of patients who regain mobility with a preserved limb. The BK/AK-ratio is not a proper measure of that. Thus, focusing solely on the BK/AK-ratio without taking into consideration the total incidence of amputation misinterprets the picture.

The current 1-year mortality rates of the patients who underwent amputation in the areas studied were high: 45% **(I)** and 52% **(II)**, respectively. In Southern Finland, the one-year mortality has increased significantly since the 1990s (Alaranta et al. 1995, Laaperi et al. 1993, Pohjolainen and Alaranta 1999). This is due to the current aggressive approach of treating even old, fragile and multidiseased patients with reconstructions **(II)**. This is also indicated by the low overall amputation rate as compared to other amputation series (Ebskov et al. 1994; Gutteridge et al. 1994; Karlstrom and Bergqvist 1997; Lindholt et al.

1994; Luther et al. 2000; Rommers et al. 1997; TASC 2000) as well as previous reports from Southern Finland (Alaranta et al. 1995; Laaperi et al. 1993; Pohjolainen and Alaranta 1988; Pohjolainen and Alaranta 1999). Other manifestations of arterial occlusive disease, mainly cardio- and cerebrovascular diseases, explain high mortality (Dormandy et al. 1999b; Luther 2003).

It is interesting that in the series of PTA-studies on CLI-patients, many studies report high limb salvage and clinical improvement rates (72-89% in 2-3 years), regardless of the generally low patency rates (Boyer et al. 2000; Lofberg et al. 1996; London et al. 1995). In our study **(IV)** the hemodynamic patency rate was also considerably low, whereas the limb salvage rate was extremely high. This indicates that in some cases the initial success of infra-inguinal PTA could be sufficient for a favourable outcome in patients with CLI. Or, one might doubt, whether all these treated patients had true CLI and what would have been the limb loss rate if these same patients had undergone no intervention other than the best medical therapy. So far, in Helsinki, the CLI patients treated with PTA have had shorter lesions than those treated with a bypass operation. The results of study **IV** support the view that PTA could be considered as a first-line treatment in a selected group of CLI-patients. However, there is clearly a need for a randomized prospective study to determine the optimal primary intervention for different kind of lesions and patients.

The implementation of a multidisciplinary team approach for the prevention and treatment of diabetic foot ulcers has been reported to be an effective means of preventing amputations in the diabetic patient (Edmonds et al. 1986; Gibbons et al. 1993; Holstein et al. 2000; Larsson et al. 1995; Morris et al. 1998; van Houtum et al. 2004). However, it is difficult or impossible to give a direct answer to the question of what caused the decrease in the amputation rate in diabetics and to what extent in the study areas; what is the exact role of vascular surgery as a part of multidisciplinary team in decreasing amputation figures. As at the same time increase in vascular surgical activity has happened throughout the world.

The incidence of major amputations in diabetic patients in Helsinki has decreased by 23% from the beginning of the 1990s (1990-1994) to the beginning of this millenium (1999-2002) **(V)**. By taking into account the prevalence of diabetes in 1990 and 2000 in Finland, the diabetes-specific incidence rates could be calculated for the study area. This gave a

33 % fall in major amputations per million individuals with diabetes during the study period. HUCH implements an aggressive policy of attempting revascularisation in all patients with CLI who have the possibility of maintaining independence with the preserved limb, presuming that the limb is salvageable and the patient´s condition allows surgical or radiological procedures. Diabetes alone never deters aggressive attempts at limb salvage.

On the basis of our results, we conclude, as do several others, that an increase in vascular reconstructions also reduces the number of major lower limb amputations in diabetic patients. The establishment of a diabetic foot team and better treatment of diabetic foot ulcers also have an important role in the prevention of amputations. Thus, this study cannot give a direct answer on the impact of vascular surgery or the work of a multidisciplinary diabetic foot team on the amputation figures; however both seem to improve results.

Finally, to ascertain the appropriate treatment methods for CLI, large, properly designed prospective randomised studies need to be performed in the near future.

11. CONCLUSIONS

1. The incidence of major amputation has decreased in the hospital region without a university hospital (Seinäjoki Central Hospital region) during recent years.
2. The incidence of major amputation has decreased in the hospital region with a university hospital (Southern Finland). The diminishing group of patients undergoing major amputation are often multimorbid. The proportion of AK-amputations has increased, mortality of the amputees is high and rehabilitation possibilities are low.
3. Infrapopliteal bypass can be considered as an index-procedure in preventing major amputations.
4. A decrease in amputation rates among elderly patients can be achieved by means of active revascularisation at least as well as in younger patients.
5. PTA can be considered as a first-line treatment in a selected group of CLI-patients, as it gives good limb salvage rates. However, there is clearly a need for a randomised prospective study to determine the optimal primary intervention for different kinds of lesions and patients, now in the gray area of uncertainty.
6. The decrease in major amputation rates among diabetic as well as nondiabetic patients can be attributed to the increased interest in amputation prevention.

12. ACKNOWLEDGEMENTS

I wish to express my gratitude and appreciation to:

My supervisor, professor Mauri Lepäntalo, for introducing me to the interesting field of vascular research. Without Mauri´s continous support, clear instructions and extensive knowledge of vascular surgery, this study would not have been possible. Mauri has always found time to teach and give advice. Besides carrying out scientific work, Mauri also sets an example as a talented surgeon and chief, who takes and gives responsibility wisely. It has been a privilege to work as a vascular trainee at his clinic for these past three years.

Antti Eskelinen, M.D., my beloved husband and respected co-worker, for his tireless help with the statistical analyses and all details relating to the computer programmes. I am indebted to him for unselfishly putting so much time and effort into my study. Antti´s ever lasting optimism, faith in me and love were the cornerstones of this work.

Mikael Luther, M.D., for sharing with me his research material for the third part of this study. I appreciate him for teaching me scientific writing and giving valuable advice, which has helped me in preparing subsequent manuscripts too.

Anders Albäck, M.D., who put his knowledge of vascular research at my disposal. I am grateful to him for astute comments, revisions in writing and many fruitful discussions.

Ari Jaakkola, M.D., for the idea of a survey of amputations, and Timo Hyytinen, M.D., for the idea of the questionnares to the amputees in Seinäjoki Central Hospital. I am thankful to both these skillful vascular suregons for their help and engouragement at the beginning of the study.

Docent Kimmo Mäkinen and Docent Timo Pohjolainen, who gave me very valuable advice, constructive criticism and encouraging support. I am deeply grateful to them for an improved manuscript.

My co-authors: Eeva-Maija Weselius, M.D., Mikael Railo,M.D., Henrik Sell, M.D., Docent Leena Kauppila, Docent Erkki Tukiainen, Ilkka Mäenpää, M.D., Juha Pitkänen, M.D., Päivi Salminen-Peltola, M.D., Suvi Leutola, M.D, Docent Aarne Kivioja, Asko Lukinmaa, M.D., Peter Brasken ,M.D., Wolf-Dieter Roth, M.D., Kimmo Lappalainen, M.D. and Pekka Keto, M.D., for their advice and contribution to my work.

Wolf-Dieter Roth, M.D., for expert advice on the radiological aspects of the fourth part of the study, and Sorjo Mätzke, M.D., for her kind help in all kinds of practical matters.

Anita Mäkelä, R.N. and Leena Sipilä, R.N., for help with data collection in the second part of this work and help with many practical things, and Mrs Leena Multanen, for help with many practical things.

Other colleagues and teachers: Pekka Aho, M.D., Marianne Jaroma, M.D., Milla Kallio, M.D., Ilkka Kantonen, M.D., Petteri Kauhanen, M.D., Juhani Kellosalo, M.D., Sani Laukontaus, M.D., Katariina Laurila, M.D., Aarno Lehtola, M.D., Maria Söderström, M.D., Pirkka Vikatmaa, M.D., Sailaritta Vuorisalo, M.D. and many others for their help and support.

Mr Barry White, for prompt and expert revision of the English text.

The nurses and staff of the Seinäjoki Central Hospital and the Meilahti hospital.

My parents Maija-Liisa and Jouko Pihlaja, for providing a loving and supportive home, and Marika Pihlaja, D.D.S., my dear sister, for guiding me during the first years in medical school and for her faithfull friendship and support.

Finally, Antti and our Aarne, for being the love and light of my life.

Karin and Einar Stroems Foundation, Instrumentarium Research Foundation, Orion Research Foundation, Pehr Oscar Klingendahl´s Foundation, Etelä-Pohjanmaan Lääkäriseura, Biomedicum Helsinki Foundation, Clinical Research Institute HUCH Ltd., The Finnish Medical Foundation, sanofi-aventis / Bristol-Myers Squibb, for financial support.

13. REFERENCES

Abou-Zamzam, A.M., Jr., Teruya, T.H., Killeen, J.D. and Ballard, J.L. Major lower extremity amputation in an academic vascular center. Ann Vasc Surg. 2003; 17: 86-90.

Ad Hoc Committee. Suggested standards for reports dealing with lower extremity ischemia. Prepared by the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery. J Vasc Surg. 1986; 4: 80-94.

AhChong, A.K., Chiu, K.M., Wong, M.W., Hui, H.K. and Yip, A.W. Diabetes and the outcome of infrainguinal bypass for critical limb ischaemia. ANZ J Surg. 2004; 74: 129-33.

Akbari, C.M., Pomposelli, F.B., Jr., Gibbons, G.W., Campbell, D.R., Pulling, M.C., Mydlarz, D. and LoGerfo, F.W. Lower extremity revascularization in diabetes: late observations. Arch Surg. 2000; 135: 452-6.

Alaranta, H., Alaranta, R., Pohjolainen, T. and Karkkainen, M. Lower limb amputees in Southern Finland. Prosthet Orthot Int. 1995; 19: 155-8.

Albers, M., Fratezi, A.C. and De Luccia, N. Assessment of quality of life of patients with severe ischemia as a result of infrainguinal arterial occlusive disease. J Vasc Surg. 1992; 16: 54-9.

Aronow, W.S. and Ahn, C. Prevalence of coexistence of coronary artery disease, peripheral arterial disease, and atherothrombotic brain infarction in men and women > or = 62 years of age. Am J Cardiol. 1994; 74: 64-5.

Aulivola, B., Hile, C.N., Hamdan, A.D., Sheahan, M.G., Veraldi, J.R., Skillman, J.J., Campbell, D.R., Scovell, S.D., LoGerfo, F.W. and Pomposelli, F.B., Jr. Major lower extremity amputation: outcome of a modern series. Arch Surg. 2004; 139: 395-9; discussion 399.

Benotmane, A., Mohammedi, F., Ayad, F., Kadi, K. and Azzouz, A. Diabetic foot lesions: etiologic and prognostic factors. Diabetes Metab. 2000; 26: 113-7.

Biancari, F., Alback, A., Kantonen, I., Luther, M. and Lepantalo, M. Predictive factors for adverse outcome of pedal bypasses. Eur J Vasc Endovasc Surg. 1999; 18: 138-43.

Biancari, F., Kantonen, I., Alback, A., Matzke, S., Luther, M. and Lepantalo, M. Limits of infrapopliteal bypass surgery for critical leg ischemia: when not to reconstruct. World J Surg. 2000; 24: 727-33.

Biancari, F., Kantonen, I., Matzke, S., Alback, A., Roth, W.D., Edgren, J. and Lepantalo, M. Infrainguinal endovascular and bypass surgery for critical leg ischemia in patients on long-term dialysis. Ann Vasc Surg. 2002; 16: 210-4.

Bloor, K. Natural history of arteriosclerosis of the lower extremities. Ann Roy Coll Surg Engl. 1961; 28: 36-52.

Bohm, G. and Al-Khaffaf, H. Thrombophilia and arterial disease. An up-to-date review of the literature for the vascular surgeon. Int Angiol. 2003; 22: 116-24.

Bolia, A., Brennan, J. and Bell, P.R. Recanalisation of femoro-popliteal occlusions: improving success rate by subintimal recanalisation. Clin Radiol. 1989; 40: 325.

Bolia, A., Miles, K.A., Brennan, J. and Bell, P.R. Percutaneous transluminal angioplasty of occlusions of the femoral and popliteal arteries by subintimal dissection. Cardiovasc Intervent Radiol. 1990; 13: 357-63.

Boyer, L., Therre, T., Garcier, J.M., Perez, N., Ravel, A., Privat, C. and Viallet, J.F. Infrapopliteal percutaneous transluminal angioplasty for limb salvage. Acta Radiol. 2000; 41: 73-7.

Bradbury, A. Angioplasty is the first-line treatment for critical limb ischaemia, Against the motion, Charing Cross, London, UK, 2003.
Bradbury, A.W., Bell, J., Lee, A.J., Prescott, R.J., Gillespie, I., Stansby, G. and Fowkes, F.G. Bypass or angioplasty for severe limb ischaemia? A Delphi Consensus Study. Eur J Vasc Endovasc Surg. 2002; 24: 411-6.
Bradbury, A.W. and Ruckley, C.V. Angioplasty for lower-limb ischaemia: time for randomised controlled trials. Lancet. 1996; 347: 277-8.
Burgess, E.M. and Matsen, F.A., 3rd. Determining amputation levels in peripheral vascular disease. J Bone Joint Surg Am. 1981; 63: 1493-7.
Burns, P.J., Mosquera, D.A. and Bradbury, A.W. Prevalence and significance of thrombophilia in peripheral arterial disease. Eur J Vasc Endovasc Surg. 2001; 22: 98-106.
Campbell, W.B., St Johnston, J.A., Kernick, V.F. and Rutter, E.A. Lower limb amputation: striking the balance. Ann R Coll Surg Engl. 1994; 76: 205-9.
CAPRIE Steering group. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996; 348: 1329-39.
Catalano, M. Epidemiology of critical limb ischaemia: North Italian data. Eur J Med. 1993; 2: 11-4.
Christensen, K.S. and Klarke, M. Transcutaneous oxygen measurement in peripheral occlusive disease. An indicator of wound healing in leg amputation. J Bone Joint Surg Br. 1986; 68: 423-6.
Cooper, L.T., Tse, T.S., Mikhail, M.A., McBane, R.D., Stanson, A.W. and Ballman, K.V. Long-term survival and amputation risk in thromboangiitis obliterans (Buerger's disease). J Am Coll Cardiol. 2004; 44: 2410-1.
Criqui, M.H. Peripheral arterial disease--epidemiological aspects. Vasc Med. 2001; 6: 3-7.
Criqui, M.H., Fronek, A., Barrett-Connor, E., Klauber, M.R., Gabriel, S. and Goodman, D. The prevalence of peripheral arterial disease in a defined population. Circulation. 1985; 71: 510-5.
Cruz, C.P., Eidt, J.F., Capps, C., Kirtley, L. and Moursi, M.M. Major lower extremity amputations at a Veterans Affairs hospital. Am J Surg. 2003; 186: 449-54.
Czerny, M., Trubel, W., Zimpfer, D., Grimm, M., Koller, R., Hofmann, W., Holzenbein, T., Polterauer, P. and Girsch, W. Limb-salvage by femoro-distal bypass and free muscle flap transfer. Eur J Vasc Endovasc Surg. 2004; 27: 635-9.
Da Silva, A., Widmer, L.K., Ziegler, H.W., Nissen, C. and Schweizer, W. The Basle longitudinal study: report on the relation of initial glucose level to baseline ECG abnormalities, peripheral artery disease, and subsequent mortality. J Chronic Dis. 1979; 32: 797-803.
Da Silva, A.F., Desgranges, P., Holdsworth, J., Harris, P.L., McCollum, P., Jones, S.M., Beard, J. and Callam, M. The management and outcome of critical limb ischaemia in diabetic patients: results of a national survey. Audit Committee of the Vascular Surgical Society of Great Britain and Ireland. Diabet Med. 1996; 13: 726-8.
Dionyssiou-Asteriou, A., Papastamatiou, M., Vatalas, I. and Bastounis, E. Serum Lp(a) lipoprotein levels in patients with atherosclerotic occlusive disease of the lower extremities. Eur J Vasc Endovasc Surg. 2000; 20: 57-60.
Donnelly, R. and Yeung, J.M. Management of intermittent claudication: the importance of secondary prevention. Eur J Vasc Endovasc Surg. 2002; 23: 100-7.

Dormandy, J., Heeck, L. and Vig, S. Acute limb ischemia. Semin Vasc Surg. 1999a; 12: 148-53.

Dormandy, J., Heeck, L. and Vig, S. The fate of patients with critical leg ischemia. Semin Vasc Surg. 1999b; 12: 142-7.

Dormandy, J., Heeck, L. and Vig, S. Major amputations: clinical patterns and predictors. Semin Vasc Surg. 1999c; 12: 154-61.

Dormandy, J., Heeck, L. and Vig, S. The natural history of claudication: risk to life and limb. Semin Vasc Surg. 1999d; 12: 123-37.

Dormandy, J., Heeck, L. and Vig, S. Predicting which patients will develop chronic critical leg ischemia. Semin Vasc Surg. 1999e; 12: 138-41.

Dorros, G., Jaff, M.R., Dorros, A.M., Mathiak, L.M. and He, T. Tibioperoneal (outflow lesion) angioplasty can be used as primary treatment in 235 patients with critical limb ischemia: five-year follow-up. Circulation. 2001; 104: 2057-62.

Dotter, C.T. and Judkins, M.P. Transluminal Treatment of Arteriosclerotic Obstruction. Description of a New Technic and a Preliminary Report of Its Application. Circulation. 1964; 30: 654-70.

Doubilet, P. and Abrams, H.L. The cost of underutilization. Percutaneous transluminal angioplasty for peripheral vascular disease. N Engl J Med. 1984; 310: 95-102.

Ebskov, L.B. Level of lower limb amputation in relation to etiology: an epidemiological study. Prosthet Orthot Int. 1992; 16: 163-7.

Ebskov, L.B. Major amputation for malignant melanoma: an epidemiological study. J Surg Oncol. 1993; 52: 89-91.

Ebskov, L.B. Trauma-related major lower limb amputations: an epidemiologic study. J Trauma. 1994; 36: 778-83.

Ebskov, L.B., Schroeder, T.V. and Holstein, P.E. Epidemiology of leg amputation: the influence of vascular surgery. Br J Surg. 1994; 81: 1600-3.

Edmonds, M.E., Blundell, M.P., Morris, M.E., Thomas, E.M., Cotton, L.T. and Watkins, P.J. Improved survival of the diabetic foot: the role of a specialized foot clinic. Q J Med. 1986; 60: 763-71.

Eickhoff, J.H. Changes in the number of lower limb amputations during a period of increasing vascular surgical activity. Results of a nation-wide study, Denmark, 1977-1990. Eur J Surg. 1993; 159: 469-73.

Esato, K., Zempo, N., M, O.h., Fujioka, K. and Kuga, T. Arterial reconstruction in elderly patients. Cardiovasc Surg. 1993; 1: 228-31.

Estes, J.M. and Pomposelli, F.B., Jr. Lower extremity arterial reconstruction in patients with diabetes mellitus. Diabet Med. 1996; 13 Suppl 1: S43-7.

European Consensus Document on CLI. European consensus document on Critical Leg Ischaemia. March 1989., Springer-Verlag, Berlin, 1990.

Faglia, E., Favales, F., Quarantiello, A., Calia, P., Clelia, P., Brambilla, G., Rampoldi, A. and Morabito, A. Angiographic evaluation of peripheral arterial occlusive disease and its role as a prognostic determinant for major amputation in diabetic subjects with foot ulcers. Diabetes Care. 1998; 21: 625-30.

Faglia, E., Mantero, M., Caminiti, M., Caravaggi, C., De Giglio, R., Pritelli, C., Clerici, G., Fratino, P., De Cata, P., Dalla Paola, L., Mariani, G., Poli, M., Settembrini, P.G., Sciangula, L., Morabito, A. and Graziani, L. Extensive use of peripheral angioplasty, particularly infrapopliteal, in the treatment of ischaemic diabetic foot ulcers: clinical results of a multicentric study of 221 consecutive diabetic subjects. J Intern Med. 2002; 252: 225-32.

Feinglass, J., Brown, J.L., LoSasso, A., Sohn, M.W., Manheim, L.M., Shah, S.J. and Pearce, W.H. Rates of lower-extremity amputation and arterial reconstruction in the United States, 1979 to 1996. Am J Public Health. 1999; 89: 1222-7.

Fogarty, T.J., Cranley, J.J., Krause, R.J., Strasser, E.S. and Hafner, C.D. A method for extraction of arterial emboli and thrombi. Surg Gynecol Obstet. 1963; 116: 241-4.

Fontaine, R., Klm, M. and Kieny, R. Die chirurgische behandlungen der peripheren durchblutungsstörungen. Helv Chir Acta. 1955; 36: 499-533.

Fowkes, F.G., Housley, E., Riemersma, R.A., Macintyre, C.C., Cawood, E.H., Prescott, R.J. and Ruckley, C.V. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. Am J Epidemiol. 1992; 135: 331-40.

Gibbons, G.W. The diabetic foot: amputations and drainage of infection. J Vasc Surg. 1987; 5: 791-3.

Gibbons, G.W. and Eiopoulos, G.M. Infection of the diabetic foot, Saunders, Philadelphia, 1995.

Gibbons, G.W., Marcaccio, E.J., Jr., Burgess, A.M., Pomposelli, F.B., Jr., Freeman, D.V., Campbell, D.R., Miller, A. and LoGerfo, F.W. Improved quality of diabetic foot care, 1984 vs 1990. Reduced length of stay and costs, insufficient reimbursement. Arch Surg. 1993; 128: 576-81.

Gouny, P., Bertrand, P., Decaix, B., Hocquet-Cheynel, C., Karcenty, B., Chemla, M. and Nussaume, O. Distal bypass for limb salvage: comparative study in patients below and above 80 years of age. J Cardiovasc Surg (Torino). 1994; 35: 419-24.

Grimer, R.J., Taminiau, A.M. and Cannon, S.R. Surgical outcomes in osteosarcoma. J Bone Joint Surg Br. 2002; 84: 395-400.

Group TG. Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia. The global lower extremity amputation study group. Br J Surg. 2000; 87: 328-37.

Gutteridge, B., Torrie, P. and Galland, B. Trends in arterial reconstruction, angioplasty and amputation. Health Trends. 1994; 26: 88-91.

Hallett, J.W., Jr., Byrne, J., Gayari, M.M., Ilstrup, D.M., Jacobsen, S.J. and Gray, D.T. Impact of arterial surgery and balloon angioplasty on amputation: a population-based study of 1155 procedures between 1973 and 1992. J Vasc Surg. 1997; 25: 29-38.

Harrington, E.B., Harrington, M.E., Schanzer, H. and Haimov, M. End-stage renal disease--is infrainguinal limb revascularization justified? J Vasc Surg. 1990; 12: 691-5; discussion 695-6.

Harris, P.L., Veith, F.J., Shanik, G.D., Nott, D., Wengerter, K.R. and Moore, D.J. Prospective randomized comparison of in situ and reversed infrapopliteal vein grafts. Br J Surg. 1993; 80: 173-6.

Hearn, A.T., Smith, J.M., Welling, R.E., Lohr, J.M. and Thibodeaux, L.C. Analysis of autogenous vein femoral-infrapopliteal bypass for limb salvage in the elderly. Cardiovasc Surg. 1996; 4: 105-9.

Heikkinen, M., The Vascular Surgical Service - Review of the 1990s and Future Prospects, Tampere University, Tampere, 2003.

Heikkinen, M.A., Salenius, J.P., Saarinen, J.P., Laurikka, J., Metsanoja, R., Zeitlin, R., Suominen, V. and Auvinen, O. Regional differences in the use of a vascular surgical service and incidence of amputations in a well-defined geographical area. Eur J Surg. 2002; 168: 724-9.

Holdsworth, J. District hospital management and outcome of critical lower limb ischaemia: comparison with national figures. Eur J Vasc Endovasc Surg. 1997; 13: 159-63.
Holm, J., Arfvidsson, B., Jivegard, L., Lundgren, F., Lundholm, K., Schersten, T., Stenberg, B., Tylen, U., Zachrisson, B.F., Lindberg, H. and et al. Chronic lower limb ischaemia. A prospective randomised controlled study comparing the 1-year results of vascular surgery and percutaneous transluminal angioplasty (PTA). Eur J Vasc Surg. 1991; 5: 517-22.
Holstein, P., Ellitsgaard, N., Olsen, B.B. and Ellitsgaard, V. Decreasing incidence of major amputations in people with diabetes. Diabetologia. 2000; 43: 844-7.
Houghton, A.D., Taylor, P.R., Thurlow, S., Rootes, E. and McColl, I. Success rates for rehabilitation of vascular amputees: implications for preoperative assessment and amputation level. Br J Surg. 1992; 79: 753-5.
Humphreys, W.V., Evans, F., Watkin, G. and Williams, T. Critical limb ischaemia in patients over 80 years of age: options in a district general hospital. Br J Surg. 1995; 82: 1361-3.
ICAI. Long-term mortality and its predictors in patients with critical leg ischaemia. The I.C.A.I. Group (Gruppo di Studio dell'Ischemia Cronica Critica degli Arti Inferiori). The Study Group of Criticial Chronic Ischemia of the Lower Exremities. Eur J Vasc Endovasc Surg. 1997; 14: 91-5.
Illuminati, G., Bertagni, A., Calio, F.G. and Papaspyropoulos, V. Distal polytetrafluoroethylene bypasses in patients older than 75 years. Arch Surg. 2000; 135: 780-4.
Illuminati, G., Calio, F.G., Bertagni, A., Piermattei, A., Vietri, F. and Martinelli, V. Results of distal revascularization in elderly patients for critical ischemia of the lower limbs. Acta Chir Belg. 1999; 99: 68-71.
International Consensus on the Diabetic Foot. International Consensus on the Diabetic Foot, Amsterdam, 1999.
Jamsen, T., Manninen, H., Tulla, H. and Matsi, P. The final outcome of primary infrainguinal percutaneous transluminal angioplasty in 100 consecutive patients with chronic critical limb ischemia. J Vasc Interv Radiol. 2002; 13: 455-63.
Jivegard, L.E., Augustinsson, L.E., Holm, J., Risberg, B. and Ortenwall, P. Effects of spinal cord stimulation (SCS) in patients with inoperable severe lower limb ischaemia: a prospective randomised controlled study. Eur J Vasc Endovasc Surg. 1995; 9: 421-5.
Johnson, B.F., Evans, L., Drury, R., Datta, D., Morris-Jones, W. and Beard, J.D. Surgery for limb threatening ischaemia: a reappraisal of the costs and benefits. Eur J Vasc Endovasc Surg. 1995; 9: 181-8.
Johnston, S.L., Lock, R.J. and Gompels, M.M. Takayasu arteritis: a review. J Clin Pathol. 2002; 55: 481-6.
Jones, L.E. Lower limb amputation in three Australian states. Int Disabil Stud. 1990; 12: 37-40.
Juergens, J.L., Barker, N.W. and Hines, E.A., Jr. Arteriosclerosis obliterans: review of 520 cases with special reference to pathogenic and prognostic factors. Circulation. 1960; 21: 188-95.
Kannel, W.B. and McGee, D.L. Update on some epidemiologic features of intermittent claudication: the Framingham Study. J Am Geriatr Soc. 1985; 33: 13-8.
Kantonen, I., Lepantalo, M., Salenius, J.P., Forsstrom, E., Hakkarainen, T., Huusari, H., Jaakkola, A., Kaarne, M., Kaartinen, P., Kivivuori, R., Kostiainen, S., Lehtonen, J.,

Loponen, P., Luther, M., Maenpaa, I., Nikula, P., Riekkinen, H., Rissanen, K., Vilkko, P. and Ylonen, K. Auditing a nationwide vascular registry--the 4-year Finnvasc experience. Finnvasc Study Group. Eur J Vasc Endovasc Surg. 1997; 14: 468-74.

Karlstrom, L. and Bergqvist, D. Effects of vascular surgery on amputation rates and mortality. Eur J Vasc Endovasc Surg. 1997; 14: 273-83.

Kavanagh, T.G., Cannon, S.R., Pringle, J., Stoker, D.J. and Kemp, H.B. Paraosteal osteosarcoma. Treatment by wide resection and prosthetic replacement. J Bone Joint Surg Br. 1990; 72: 959-65.

Kazmers, A., Perkins, A.J. and Jacobs, L.A. Major lower extremity amputation in Veterans Affairs medical centers. Ann Vasc Surg. 2000; 14: 216-22.

Kellicut, D.C., 3rd, Sidawy, A.N. and Arora, S. Diabetic vascular disease and its management. Semin Vasc Surg. 2003; 16: 12-8.

Klomp, H.M., Spincemaille, G.H., Steyerberg, E.W., Habbema, J.D. and van Urk, H. Spinal-cord stimulation in critical limb ischaemia: a randomised trial. ESES Study Group. Lancet. 1999; 353: 1040-4.

Klomp, H.M. and Steyerberg, E.W. Systematic review and meta-analysis of controlled trials assessing spinal cord stimulation for inoperable critical leg ischaemia, author reply. Br J Surg. 2005; 92: 120; author reply 120-1.

Korn, P., Hoenig, S.J., Skillman, J.J. and Kent, K.C. Is lower extremity revascularization worthwhile in patients with end-stage renal disease? Surgery. 2000; 128: 472-9.

Kroger, K., Suckel, A., Hirche, H. and Rudofsky, G. Different prevalence of asymptomatic atherosclerotic lesions in males and females. Vasc Med. 1999; 4: 61-5.

Krupski, W.C. Overview of extremity amputations. In: R.B. Rutherford, P. Gloviczki, K.W. Johnston, R.F. Kempczinski and W.C. Krupski (Eds.), Vascular Surgery, Vol. 2, Saunders, Denver, 2000, pp. 2175-84.

Kuukasjarvi, P. and Salenius, J.P. Perioperative outcome of acute lower limb ischaemia on the basis of the national vascular registry. The Finnvasc Study Group. Eur J Vasc Surg. 1994; 8: 578-83.

Laakso, M., Reunanen, A., Klaukka, T., Aromaa, A., Maatela, J. and Pyorala, K. Changes in the prevalence and incidence of diabetes mellitus in Finnish adults, 1970-1987. Am J Epidemiol. 1991; 133: 850-7.

Laaperi, T., Pohjolainen, T., Alaranta, H. and Karkkainen, M. Lower-limb amputations. Ann Chir Gynaecol. 1993; 82: 183-7.

Larsson, J., Apelqvist, J., Agardh, C.D. and Stenstrom, A. Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach? Diabet Med. 1995; 12: 770-6.

Laxdal, E., Jenssen, G.L., Pedersen, G. and Aune, S. Subintimal angioplasty as a treatment of femoropopliteal artery occlusions. Eur J Vasc Endovasc Surg. 2003; 25: 578-82.

Le Hello, C., Levesque, H., Jeanton, M., Cailleux, N., Galateau, F., Peillon, C., Veyssier, P., Watelet, J., Letellier, P., Courtois, H. and Maiza, D. Lower limb giant cell arteritis and temporal arteritis: followup of 8 cases. J Rheumatol. 2001; 28: 1407-12.

Leather, R.P., Shah, D.M., Chang, B.B. and Kaufman, J.L. Resurrection of the in situ saphenous vein bypass. 1000 cases later. Ann Surg. 1988; 208: 435-42.

Lepantalo, M., Biancari, F. and Tukiainen, E. Never amputate without consultation of a vascular surgeon. Diabetes Metab Res Rev. 2000; 16 Suppl 1: S27-32.

Lepantalo, M. and Matzke, S. Outcome of unreconstructed chronic critical leg ischaemia. Eur J Vasc Endovasc Surg. 1996; 11: 153-7.
Lepantalo, M., Vuorisalo, S. and Lassila, R. Unexpected causes of acute lower limb ischemia. In: J.N. Branchereaua (Ed.), Unexpected challenges in vascular surgery, Blackwell futura, Oxford, 2005, pp. 185194.

Liedberg, E. and Persson, B.M. Age, diabetes and smoking in lower limb amputation for arterial occlusive disease. Acta Orthop Scand. 1983; 54: 383-8.
Lindholt, J.S., Bovling, S., Fasting, H. and Henneberg, E.W. Vascular surgery reduces the frequency of lower limb major amputations. Eur J Vasc Surg. 1994; 8: 31-5.

Lofberg, A.M., Karacagil, S., Ljungman, C., Westman, B., Bostrom, A., Hellberg, A. and Ostholm, G. Percutaneous transluminal angioplasty of the femoropopliteal arteries in limbs with chronic critical lower limb ischemia. J Vasc Surg. 2001; 34: 114-21.
Lofberg, A.M., Lorelius, L.E., Karacagil, S., Westman, B., Almgren, B. and Berqgvist, D. The use of below-knee percutaneous transluminal angioplasty in arterial occlusive disease causing chronic critical limb ischemia. Cardiovasc Intervent Radiol. 1996; 19: 317-22.
LoGerfo, F.W. and Marcaccio, E.J. Etiology and assessment of ischemia in the diabetic. Ann Chir Gynaecol. 1992; 81: 122-4.
London, N.J., Srinivasan, R., Naylor, A.R., Hartshorne, T., Ratliff, D.A., Bell, P.R. and Bolia, A. Subintimal angioplasty of femoropopliteal artery occlusions: the long-term results. Eur J Vasc Surg. 1994; 8: 148-55.
London, N.J., Varty, K., Sayers, R.D., Thompson, M.M., Bell, P.R. and Bolia, A. Percutaneous transluminal angioplasty for lower-limb critical ischaemia. Br J Surg. 1995; 82: 1232-5.
Lundberg, G., Markers of tissue ischaemia in lower limb arterial insufficiency
- an experimental and clinical study, Department of Surgical Sciences, Karolinska Institute, Stockholm, 2005.
Luther, M. The influence of arterial reconstructive surgery on the outcome of critical leg ischaemia. Eur J Vasc Surg. 1994; 8: 682-9.
Luther, M. Treatment of chronic critical leg ischaemia--a cost benefit analysis. Ann Chir Gynaecol Suppl. 1997; 213: 1-142.
Luther, M. Klaudikation, kritisk iskemi och livskvalitet. Finska Läkaresällskapets Handlingar. 2002; 162(2): 14-19.
Luther, M. Fate of the patient with chronic limb ischaemia, The 7th Annual Meeting of the Scandinavian Association for Vascular Surgery, Tampere, Finland, 2003.
Luther, M., Kantonen, I., Lepantalo, M., Salenius, J. and Group, K.Y. Arterial intervention and reduction in amputation for chronic critical leg ischaemia. Br J Surg. 2000; 87: 454-8.
Luther, M. and Lepantalo, M. Femoropopliteal reconstructions--influence of risk factors on outcome. Ann Chir Gynaecol. 1996; 85: 238-46.
Luther, M. and Lepantalo, M. Arterial reconstruction to the foot arteries--a viable option? Eur J Surg. 1997a; 163: 659-65.
Luther, M. and Lepantalo, M. Femorotibial reconstructions for chronic critical leg ischaemia: influence on outcome by diabetes, gender and age. Eur J Vasc Endovasc Surg. 1997b; 13: 569-77.
Luther, M., Lepantalo, M., Alback, A. and Matzke, S. Amputation rates as a measure of vascular surgical results. Br J Surg. 1996; 83: 241-4.

Marcoux, R.M., Larrat, E.P., Taubman, A.H. and Wilson, J. Screening for peripheral arterial disease. J Am Pharm Assoc (Wash). 1996; NS36: 370-3.
Matsagas, M.I., Rivera, M.A., Tran, T., Mitchell, A., Robless, P., Davies, A.H. and Geroulakos, G. Clinical outcome following infra-inguinal percutaneous transluminal angioplasty for critical limb ischemia. Cardiovasc Intervent Radiol. 2003; 26: 251-5.
Matsi, P. Percutaneous transluminal angioplasty in critical limb ischaemia. Ann Chir Gynaecol. 1995; 84: 359-62.

Matsubara, J., Sakamoto, S., Shikata, H., Hida, K., Kobayashi, M., Kobata, T. and Kurose, K. Is arterial surgery advisable for patients over 80 years of age? J Cardiovasc Surg (Torino). 2001; 42: 375-9.

Mattes, E., Norman, P.E. and Jamrozik, K. Falling incidence of amputations for peripheral occlusive arterial disease in Western Australia between 1980 and 1992. Eur J Vasc Endovasc Surg. 1997; 13: 14-22.
Matzke, S. and Lepantalo, M. Claudication does not always precede critical leg ischemia. Vasc Med. 2001; 6: 77-80.
McDermott, M.M., Greenland, P., Liu, K., Criqui, M.H., Guralnik, J.M., Celic, L. and Chan, C. Sex differences in peripheral arterial disease: leg symptoms and physical functioning. J Am Geriatr Soc. 2003; 51: 222-8.
McLoughlin, R.F., Fitzgerald, L.P. and O'Donnell, J.A. Limb salvage in the elderly. Ann Vasc Surg. 1989; 3: 11-3.
McWhinnie, D.L., Gordon, A.C., Collin, J., Gray, D.W. and Morrison, J.D. Rehabilitation outcome 5 years after 100 lower-limb amputations. Br J Surg. 1994; 81: 1596-9.
Meier, R.H. Rehabilitation of the person with an amputation. In: R.B. Rutherford, J.L. Cronenwett, P. Gloviczki, K.W. Johnston, R.F. Kempczinski and W.C. Krupski (Eds.), Vascular surgery, Vol. 2, Saunders, Denver, 2000, pp. 2227-48.
Meyerson, S.L., Skelly, C.L., Curi, M.A., Desai, T.R., Katz, D., Bassiouny, H.S., McKinsey, J.F., Gewertz, B.L. and Schwartz, L.B. Long-term results justify autogenous infrainguinal bypass grafting in patients with end-stage renal failure. J Vasc Surg. 2001; 34: 27-33.
Mills, J.L., Sr. Buerger's disease in the 21st century: diagnosis, clinical features, and therapy. Semin Vasc Surg. 2003; 16: 179-89.
Mills, J.L., Taylor, L.M., Jr. and Porter, J.M. Buerger's disease in the modern era. Am J Surg. 1987; 154: 123-9.
Molloy, K.J., Nasim, A., London, N.J., Naylor, A.R., Bell, P.R., Fishwick, G., Bolia, A. and Thompson, M.M. Percutaneous transluminal angioplasty in the treatment of critical limb ischemia. J Endovasc Ther. 2003; 10: 298-303.
Moniz, M.P., Ombrellaro, M.P., Stevens, S.L., Freeman, M.B., Diamond, D.L. and Goldman, M.H. Concomitant orthopedic and vascular injuries as predictors for limb loss in blunt lower extremity trauma. Am Surg. 1997; 63: 24-8.
Moran, S.L., Illig, K.A., Green, R.M. and Serletti, J.M. Free-tissue transfer in patients with peripheral vascular disease: a 10-year experience. Plast Reconstr Surg. 2002; 109: 999-1006.
Morris, A.D., McAlpine, R., Steinke, D., Boyle, D.I., Ebrahim, A.R., Vasudev, N., Stewart, C.P., Jung, R.T., Leese, G.P., MacDonald, T.M. and Newton, R.W. Diabetes and lower-limb amputations in the community. A retrospective cohort study. DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland/Medicines Monitoring Unit. Diabetes Care. 1998; 21: 738-43.

Murabito, J.M., D'Agostino, R.B., Silbershatz, H. and Wilson, W.F. Intermittent claudication. A risk profile from The Framingham Heart Study. Circulation. 1997; 96: 44-9.

Mätzke, S., Identification and outcome of critical leg ischaemia, Helsinki University, Helsinki, 2004.

Nasr, M.K., McCarthy, R.J., Hardman, J., Chalmers, A. and Horrocks, M. The increasing role of percutaneous transluminal angioplasty in the primary management of critical limb ischaemia. Eur J Vasc Endovasc Surg. 2002; 23: 398-403.

Nehler, M.R., Moneta, G.L., Edwards, J.M., Yeager, R.A., Taylor, L.M., Jr. and Porter, J.M. Surgery for chronic lower extremity ischemia in patients eighty or more years of age: operative results and assessment of postoperative independence. J Vasc Surg. 1993; 18: 618-24; discussion 624-6.

Norgren, L., Alwmark, A., Angqvist, K.A., Hedberg, B., Bergqvist, D., Takolander, R., Claes, G., Lundell, A., Holm, J., Jivegard, L. and et al. A stable prostacyclin analogue (iloprost) in the treatment of ischaemic ulcers of the lower limb. A Scandinavian-Polish placebo controlled, randomised multicenter study. Eur J Vasc Surg. 1990; 4: 463-7.

O'Mara, C.S., Kilgore, T.L., Jr., McMullan, M.H., Maples, M.D., Hollingsworth, J.F. and Tyler, H.B. Distal bypass for limb salvage in very elderly patients. Am Surg. 1987; 53: 66-70.

Onkamo, P., Vaananen, S., Karvonen, M. and Tuomilehto, J. Worldwide increase in incidence of Type I diabetes--the analysis of the data on published incidence trends. Diabetologia. 1999; 42: 1395-403.

Ostrup, L.T. and Vilkki, S.K. Reconstructive microsurgery--a review. Acta Orthop Scand. 1986; 57: 395-401.

Ouriel, K. Thrombolysis or operation for peripheral arterial occlusion. Vasc Med. 1996; 1: 159-61.

Ouriel, K., Fiore, W.M. and Geary, J.E. Limb-threatening ischemia in the medically compromised patient: amputation or revascularization? Surgery. 1988; 104: 667-72.

Ouriel, K., Shortell, C.K., DeWeese, J.A., Green, R.M., Francis, C.W., Azodo, M.V., Gutierrez, O.H., Manzione, J.V., Cox, C. and Marder, V.J. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. J Vasc Surg. 1994; 19: 1021-30.

Parsons, R.E., Suggs, W.D., Lee, J.J., Sanchez, L.A., Lyon, R.T. and Veith, F.J. Percutaneous transluminal angioplasty for the treatment of limb threatening ischemia: do the results justify an attempt before bypass grafting? J Vasc Surg. 1998; 28: 1066-71.

Pell, J.P., Donnan, P.T., Fowkes, F.G. and Ruckley, C.V. Quality of life following lower limb amputation for peripheral arterial disease. Eur J Vasc Surg. 1993; 7: 448-51.

Pell, J.P., Fowkes, F.G., Ruckley, C.V., Clarke, J., Kendrick, S. and Boyd, J.H. Declining incidence of amputation for arterial disease in Scotland. Eur J Vasc Surg. 1994; 8: 602-6.

Pell, J.P. and Fowkes, F.G.R. Risk factors for critical limb ischaemia. Epidemiol Update. 1997; 2: 19-25.

Peltonen, S., Biancari, F., Lindgren, L., Makisalo, H., Honkanen, E. and Lepantalo, M. Outcome of infrainguinal bypass surgery for critical leg ischaemia in patients with chronic renal failure. Eur J Vasc Endovasc Surg. 1998; 15: 122-7.

Pezzin, L.E., Dillingham, T.R. and MacKenzie, E.J. Rehabilitation and the long-term outcomes of persons with trauma-related amputations. Arch Phys Med Rehabil. 2000; 81: 292-300.
Pohjolainen, T., The Finnish lower-limb amputee, Helsinki University, Helsinki, 1991.
Pohjolainen, T. and Alaranta, H. Lower limb amputations in southern Finland 1984-1985. Prosthet Orthot Int. 1988; 12: 9-18.
Pohjolainen, T. and Alaranta, H. Epidemiology of lower limb amputees in Southern Finland in 1995 and trends since 1984. Prosthet Orthot Int. 1999; 23: 88-92.
Pohjolainen, T., Alaranta, H. and Karkkainen, M. Prosthetic use and functional and social outcome following major lower limb amputation. Prosthet Orthot Int. 1990; 14: 75-9.

Pomposelli, F.B., Jr., Arora, S., Gibbons, G.W., Frykberg, R., Smakowski, P., Campbell, D.R., Freeman, D.V. and LoGerfo, F.W. Lower extremity arterial reconstruction in the very elderly: successful outcome preserves not only the limb but also residential status and ambulatory function. J Vasc Surg. 1998; 28: 215-25.

Pomposelli, F.B., Jr., Jepsen, S.J., Gibbons, G.W., Campbell, D.R., Freeman, D.V., Miller, A. and LoGerfo, F.W. Efficacy of the dorsal pedal bypass for limb salvage in diabetic patients: short-term observations. J Vasc Surg. 1990; 11: 745-51; discussion 751-2.
Pomposelli, F.B., Jr., Marcaccio, E.J., Gibbons, G.W., Campbell, D.R., Freeman, D.V., Burgess, A.M., Miller, A. and LoGerfo, F.W. Dorsalis pedis arterial bypass: durable limb salvage for foot ischemia in patients with diabetes mellitus. J Vasc Surg. 1995; 21: 375-84.
Reekers, J.A. Percutaneous intentional extraluminal (subintimal) revascularization (PIER) for critical lower limb ischemia: too good to be true? J Endovasc Ther. 2002; 9: 419-21.
Reekers, J.A. and Bolia, A. Percutaneous intentional extraluminal (subintimal) recanalization: how to do it yourself. Eur J Radiol. 1998; 28: 192-8.
Reifsnyder, T., Grossman, J.P. and Leers, S.A. Limb loss after lower extremity bypass. Am J Surg. 1997; 174: 149-51.
Reunanen, A., Takkunen, H. and Aromaa, A. Prevalence of intermittent claudication and its effect on mortality. Acta Med Scand. 1982; 211: 249-56.
Rommers, G.M., Vos, L.D., Groothoff, J.W., Schuiling, C.H. and Eisma, W.H. Epidemiology of lower limb amputees in the north of The Netherlands: aetiology, discharge destination and prosthetic use. Prosthet Orthot Int. 1997; 21: 92-9.
Rutherford, R.B., Baker, J.D., Ernst, C., Johnston, K.W., Porter, J.M., Ahn, S. and Jones, D.N. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997; 26: 517-38.
Salas, C. and Bolia, A. Angioplasty is the first-line treatment in critical limb ischaemia, for the motion, Charing Cross, London, UK, 2003.
Salenius, J.P., Lepantalo, M., Ylonen, K. and Luther, M. Treatment of peripheral vascular diseases--basic data from the nationwide vascular registry FINNVASC. Ann Chir Gynaecol. 1993; 82: 235-40.
Sayers, R.D., Raptis, S., Berce, M. and Miller, J.H. Long-term results of femorotibial bypass with vein or polytetrafluoroethylene. Br J Surg. 1998; 85: 934-8.
Sayers, R.D., Thompson, M.M., Hartshorne, T., Budd, J.S. and Bell, P.R. Treatment and outcome of severe lower-limb ischaemia. Br J Surg. 1994; 81: 521-3.

Sayers, R.D., Thompson, M.M., London, N.J., Varty, K., Naylor, A.R., Budd, J.S., Ratliff, D.A. and Bell, P.R. Selection of patients with critical limb ischaemia for femorodistal vein bypass. Eur J Vasc Surg. 1993; 7: 291-7.
Scher, L.A., Veith, F.J., Ascer, E., White, R.A., Samson, R.H., Sprayregen, S. and Gupta, S.K. Limb salvage in octogenarians and nonagenarians. Surgery. 1986; 99: 160-5.
Second European Consensus Document. Second European Consensus Document on chronic critical leg ischemia. Eur J Vasc Surg. 1992; 6 Suppl A: 1-32.
Shearman, C.P., Beard, J.D. and Gaines, P.A. Treatment of chronic lower limb ischaemia. In: J.D. Beard and P.A. Gaines (Eds.), Saunders, London, 2000, pp. 47-81.
Shigematsu, H. and Shigematsu, K. Factors affecting the long-term outcome of Buerger's disease (thromboangiitis obliterans). Int Angiol. 1999; 18: 58-64.
Smith, I., Franks, P.J., Greenhalgh, R.M., Poulter, N.R. and Powell, J.T. The influence of smoking cessation and hypertriglyceridaemia on the progression of peripheral arterial disease and the onset of critical ischaemia. Eur J Vasc Endovasc Surg. 1996; 11: 402-8.
Solonen, K.A. and Huittinen, V.M. Amputaatiot ja proteesit, Proteesisäätiö, Helsinki, 1991.
Spinosa, D.J., Leung, D.A., Matsumoto, A.H., Bissonette, E.A., Cage, D., Harthun, N.L., Kern, J.A., Angle, J.F., Hagspiel, K.D., Crosby, I.K., Wellons, H.A., Jr., Tribble, C.G. and Hartwell, G.D. Percutaneous intentional extraluminal recanalization in patients with chronic critical limb ischemia. Radiology. 2004; 232: 499-507.
Steck, A. and Rewers, M. Epidemiology and geography of type I diabetes mellitus. In: R.A. DeFronzo, E. Ferranini, H. Keen and P. Zimmet (Eds.), Textbook of diabetes mellitus, Chichester, West Sussex, 2004.
Sweetnam, R. Osteosarcoma. Ann R Coll Surg Engl. 1969; 44: 38-58.
Sweetnam, R. The diminishing role of amputation in the management of malignant tumours of bone. Ann R Coll Surg Engl. 1991; 73: 165-9.
Sweetnam, R., Knowelden, J. and Seddon, H. Bone sarcoma: treatment by irradiation, amputation, or a combination of the two. Br Med J. 1971; 2: 363-7.
TASC. Management of peripheral arterial disease (PAD). TransAtlantic Inter-Society Consensus (TASC). Eur J Vasc Endovasc Surg. 2000; 19 Suppl A: Si-xxviii, S1-250.
Taylor, L.M., Jr., Hamre, D., Dalman, R.L. and Porter, J.M. Limb salvage vs amputation for critical ischemia. The role of vascular surgery. Arch Surg. 1991; 126: 1251-7; discussion 1257-8.
The Oral Iloprost in severe Leg Ischaemia Study Group. Two randomised and placebo-controlled studies of an oral prostacyclin analogue (Iloprost) in severe leg ischaemia. The Oral Iloprost in severe Leg Ischaemia Study Group. Eur J Vasc Endovasc Surg. 2000; 20: 358-62.
The U.K. Severe Limb Ischaemia Study Group. Treatment of limb threatening ischaemia with intravenous iloprost: a randomised double-blind placebo controlled study. U.K. Severe Limb Ischaemia Study Group. Eur J Vasc Surg. 1991; 5: 511-6.
The Vascular Surgical Society of Great Britain and Ireland. Critical limb ischaemia: management and outcome. Report of a national survey. The Vascular Surgical Society of Great Britain and Ireland. Eur J Vasc Endovasc Surg. 1995; 10: 108-13.
Tisi, P.V., Mirnezami, A., Baker, S., Tawn, J., Parvin, S.D. and Darke, S.G. Role of subintimal angioplasty in the treatment of chronic lower limb ischaemia. Eur J Vasc Endovasc Surg. 2002; 24: 417-22.
Tukiainen, E., Biancari, F. and Lepantalo, M. Lower limb revascularization and free flap transfer for major ischemic tissue loss. World J Surg. 2000; 24: 1531-6.

Tunis, S.R., Bass, E.B. and Steinberg, E.P. The use of angioplasty, bypass surgery, and amputation in the management of peripheral vascular disease. N Engl J Med. 1991; 325: 556-62.
Turney, B.W., Kent, S.J., Walker, R.T. and Loftus, I.M. Amputations: no longer the end of the road. J R Coll Surg Edinb. 2001; 46: 271-3.
Wahlberg, E., Lepner, U. and Olofsson, P. Limb loss in association with vascular surgery--a five-year series of major lower-limb amputation. Eur J Surg. 1994; 160: 561-7.
Van Damme, H., De Leval, L., Creemers, E. and Limet, R. Thrombangiitis obliterans (Buerger's disease): still a limb threatening disease. Acta Chir Belg. 1997; 97: 229-36.
van Houtum, W.H., Rauwerda, J.A., Ruwaard, D., Schaper, N.C. and Bakker, K. Reduction in diabetes-related lower-extremity amputations in The Netherlands: 1991-2000. Diabetes Care. 2004; 27: 1042-6.

Vanoli, M., Bacchiani, G., Origg, L. and Scorza, R. Takayasu's arteritis: a changing disease. J Nephrol. 2001; 14: 497-505.
Varty, K., Nydahl, S., Nasim, A., Bolia, A., Bell, P.R. and London, J.M. Results of surgery and angioplasty for the treatment of chronic severe lower limb ischaemia. Eur J Vasc Endovasc Surg. 1998; 16: 159-63.

Vermassen, F.E. and van Landuyt, K. Combined vascular reconstruction and free flap transfer in diabetic arterial disease. Diabetes Metab Res Rev. 2000; 16 Suppl 1: S33-6.
Vig, S., Chitolie, A., Sleight, S., Bevan, D., Dormandy, J., Thompson, M.M. and Halliday, A. Prevalence and risk of thrombophilia defects in vascular patients. Eur J Vasc Endovasc Surg. 2004; 28: 124-31.
Wilson, S.E., Wolf, G.L. and Cross, A.P. Percutaneous transluminal angioplasty versus operation for peripheral arteriosclerosis. Report of a prospective randomized trial in a selected group of patients. J Vasc Surg. 1989; 9: 1-9.
Winell, K. The National Hospital Registry data on lower limb amputations quality indicator for diabetes care?, XIX Annual Meeting of the European Society for Vascular Surgery, Helsinki, Finland, 2005.
Virkkunen, J., Heikkinen, M., Lepantalo, M., Metsanoja, R. and Salenius, J.P. Diabetes as an independent risk factor for early postoperative complications in critical limb ischemia. J Vasc Surg. 2004; 40: 761-7.
Witso, E. and Ronningen, H. Lower limb amputations: registration of all lower limb amputations performed at the University Hospital of Trondheim, Norway, 1994-1997. Prosthet Orthot Int. 2001; 25: 181-5.
Wolfe, J.H. and Wyatt, M.G. Critical and subcritical ischaemia. Eur J Vasc Endovasc Surg. 1997; 13: 578-82.
Wolfe, J.N. Defining the outcome of critical ischaemia: a one year prospective study. Br J Surg. 1986; 73: 321.
Wolfle, K.D., Bruijnen, H., Loeprecht, H., Rumenapf, G., Schweiger, H., Grabitz, K., Sandmann, W., Lauterjung, L., Largiader, J., Erasmi, H., Kasprzak, P.M., Raithel, D., Allenberg, J.R., Lauber, A., Berlakovich, G.M., Kretschmer, G., Hepp, W., Becker, H.M. and Schulz, A. Graft patency and clinical outcome of femorodistal arterial reconstruction in diabetic and non-diabetic patients: results of a multicentre comparative analysis. Eur J Vasc Endovasc Surg. 2003; 25: 229-34.

Yeager, R.A., Moneta, G.L., Taylor, L.M., Jr., Hamre, D.W., McConnell, D.B. and Porter, J.M. Surgical management of severe acute lower extremity ischemia. J Vasc Surg. 1992; 15: 385-91; discussion 392-3.
Yilmaz, S., Sindel, T., Yegin, A. and Luleci, E. Subintimal angioplasty of long superficial femoral artery occlusions. J Vasc Interv Radiol. 2003; 14: 997-1010.
Zarins, C.K., Lu, C.T., McDonnell, A.E. and Whitehouse, W.M., Jr. Limb salvage by percutaneous transluminal recanalization of the occluded superficial femoral artery. Surgery. 1980; 87: 701-8.
Zdanowski, Z., Troeng, T. and Norgren, L. Outcome and influence of age after infrainguinal revascularisation in critical limb ischaemia. The Swedish Vascular Registry. Eur J Vasc Endovasc Surg. 1998; 16: 137-41.

14. ORIGINAL PUBLICATIONS