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IDENTIFICATION AND OUTCOME OF CRITICAL LEG ISCHAEMIA

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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 Mätzke S, Franckena M, Albäck A, Railo M, Lepäntalo M. Ankle brachial index measurements in critical leg ischaemia – the influence of experience on reproducibility. Scand J Surg 2003; 92: 144-147.

II Mätzke S, Lepäntalo M. Predictive value of distal pressure measurements in critical leg ischaemia. Ann Chir Gynaecol 1996; 85: 316-321.

III Mätzke S, Lepäntalo M. Claudication does not always precede critical leg ischaemia. Vasc Med 2001; 6: 77-80.

IV Lepäntalo M, Mätzke S. Outcome of unreconstructed chronic critical leg ischaemia. Eur J Vasc Endovasc Surg 1996; 11: 153-157.

V Mätzke S, Linna M, Mäenpää I, Pitkänen J, Sell H, Kekomäki M, Brommels M, Lepäntalo M. Surgery for critical leg ischaemia in a well defined population in Uusimaa, Finland 1991-1997 – a comparison between centralised and decentralised service models. World Journal of Surgery, submitted

3. ABBREVIATIONS

ABI	ankle brachial pressure index
AGE	advanced glycation endproduct
AMI	acute myocardial infarction
CCS	Canadian Cardiovacular Society
CHD	coronary heart disease
CLI	critical leg ischaemia
CW-Doppler	continuous wave Doppler
DD	duplex Doppler
DSA	digital subtraction angiography
eNOS	endothelial nitric oxide synthase
HBA_1	glycosylated haemoglobin
HUCH	Helsinki University Central Hospital
IC	intermittent claudication
MRI	magnetic resonance imaging
NA	not available
NYHA	New York Heart Association Functional Class
PAD	peripheral arterial disease
PRIND	prolonged reversible ischaemic neurological deficit
PVR	pulse volume recording
TBI	toe brachial pressure index
$TcPO_2$	transcutaenous oxygen tension
TFI	transfer function index
TIA	transient ischaemic attack

4. ABSTRACT

Introduction: Critical leg ischaemia is a manifestation of the atherosclerotic disease and reflects the state of the whole vascular tree. If no prodromal symptoms have been present, critical leg ischaemia may be difficult to distinguish from other complaints with similar symptoms. This study will show that up to one third of patients may experience critical leg ischaemia as the first manifestation of vascular disease. This should be taken into consideration both in the clinical assessment and epidemiological estimations.

Aim of the study: The aim of this study was to assess the clinical course of peripheral arterial disease leading to critical leg ischaemia, to assess the accuracy of basic pressure measurements in critically ischaemic patients and to evaluate the role of pressure measurement in predicting major amputation risk. Furthermore the outcome of critically ischaemic patients in a selected patient population as well as on population basis was to be studied. The influence on regional differences and referral model on amputation risk was assessed.

Methods:
The study was divided into five parts:
1. The variability of pressure measurements in CLI-patients was assessed when measured by inexperienced (22 legs) and experienced (33 legs) personnel.
2. In 110 critically ischaemic patients treated conservatively, the predictive value of ankle and toe pressure measurements and ankle brachial indices in terms of major amputation risk was assessed.
3. The duration of the symptoms preceding and indicating critical leg ischaemia was recorded in 100 patients referred to the vascular surgical clinic.
4. The outcome in 105 conservatively treated critical leg ischaemia-patients was investigated retrospectively using hospital records and death certificates.
5. The revascularisations of CLI-patients as well as age and sex-standardised amputation incidences in the Uusimaa hospital district during 7 years were assessed on registry basis.

Results:
1. Interobserver agreement between experienced measurers proved to be good while measurements performed by inexperienced measurers showed considerable variation.
2. Ankle and toe pressure measurements or ankle brachial indices performed by experienced measurers on critically ischaemic patients not suitable for reconstruction, showed no clear cut-off levels for subsequent major amputation risk and predictive value proved to be poor.
3. A considerable proportion (37%) of the patients with critical leg ischaemia presenting to the vascular surgical clinic had not experienced symptoms of claudication prior to developing critical leg ischaemia
4. In a population of conservatively treated critically patients the cumulative leg preservation was 54% at one year. Cumulative survival was 46%, and 28% of the patients were alive with a preserved leg.
5. The amputation incidences showed considerable variation throughout the study years. No clear differences could be found between populations treated in different health care models. In fact, the implementation of these models was discovered to be poor, as a large proportion of critically ischaemic patients were never subjected to vascular surgical evaluation before major amputation.

Conclusions:

To identify CLI-patients, objective assessment methods such as ankle systolic pressure measurements are needed. In our study untrained measurers achieved widely varying pressure values in critically ischaemic patients while the measurements performed by skilled vascular technicians were all within acceptable variability. Therefore experienced nurses or technicians should perform ABI measurements in order to achieve reproducible results.

Still, pressure measurements alone are not enough to determine the major amputation risk of critically ischaemic patients, as confirmed in this study. Although low pressures are associated with higher amputation risk, no cut-off values could be determined. Therefore ABI-measurements can only be used as supplementary information to clinical judgement when assessing leg viability.

Overall, critical leg ischaemia has a very poor prognosis. If surgical, or endovascular, improvement of the blood supply to the leg is not provided in due course; half of the legs will be amputated within a year. A high mortality is an additional issue in critically ischaemic patients, due to the involvement of the whole vascular tree. More than two thirds may lose either their life or their leg within one year after diagnosis. Critical leg ischaemia should be regarded as a predictor of an adverse outcome to the patient or the limb.

One of the main goals of vascular surgery is to prevent major amputations in order to enable the patients to keep their independence and mobility for their remaining lifetime. In order to avoid unnecessary amputations, it is important to direct sufficient vascular treatment on time to those patients potentially benefiting from reconstructive measures. Each municipality has to decide how to provide their population with the necessary treatment. Different treatment models have been designed in order to cut down costs and to provide services in the most efficient way. The proper implementation of these models is a prerequisite to achieving better results in the treatment of critical leg ischaemia, as well as evaluating each model’s success.

5. INTRODUCTION

Atherothrombotic disease comprises both the atherosclerotic process of the arterial wall and the thrombotic process within the artery. Although it is mainly caused by atherosclerosis, alterations of the blood flow as well as coagulation disorders affect the development and progression of the disease. It is a common disease in the industrialised world and, by affecting a major proportion of the population, is the most significant health problem in the western world (Vogt 1992). Diseases developing on the basis of general atherosclerosis are among the leading death causes (Statistical Yearbook of Finland 2000).

The changing age structure in western civilisations, due to higher life expectancy and lower birth rates, causes atherothrombotic disease to be a growing burden on the narrowing resources of our health care and social systems. The conditions arising from arterial occlusive disease affect the functional status in several fields of life both for the individual and for society. Atherothrombotic disease causes considerable morbidity and mortality (Statistical Yearbook of Finland 2000). It thus has an impact on national economies especially as the population structure changes in industrialised nations. Early diagnosis of one of the manifestations of atherothrombotic disease in the coronary arteries, carotid arteries or arteries feeding the lower limbs, makes early intervention possible, facilitating treatment as well as prevention of other manifestations (Favilli 1998).

The prevalence of symptomatic arterial occlusive disease in the lower extremities has been shown to be between 1,2 - 6,6% (Bainton 1994, Stoffers 1996) from the 5th decade of life onwards, while the proportion of asymptomatic arterial occlusive disease is estimated to be two thirds of the total amount of PAD (da Silva 1990). Critical leg ischaemia is the most severe form of arteriosclerosis in the leg, with arterial circulation impaired to an extent that it endangers the viability of the leg (Second European Consensus Document 1992, TASC 2000). It warrants treatment to avoid major amputation, which in most of the cases results in loss of functional ability frequently leading to hospitalisation.

Therefore the treatment of critical leg ischaemia (CLI) is one of the most important tasks for vascular surgery. Although only 5% of symptomatic arterial occlusive disease in the lower limb is estimated to become critically ischaemic (TASC 2000), the workload caused by CLI in vascular surgical units is disproportionately high. CLI accounts for a major part (35%) of vascular surgical activity in Finland (Luther 2000).

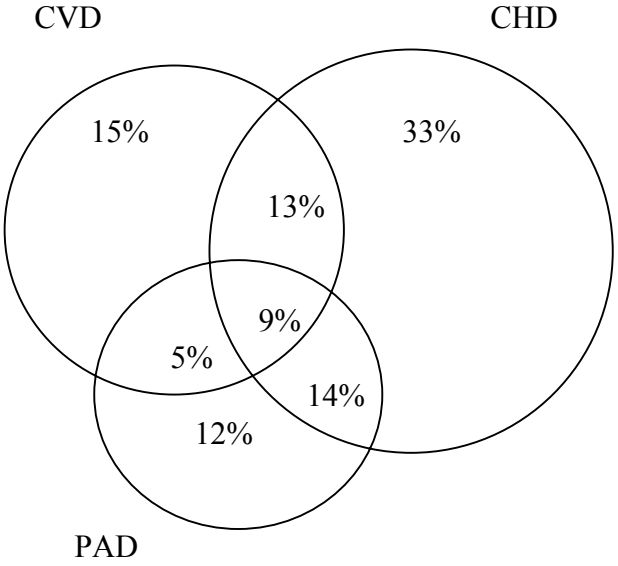
6. REVIEW OF THE LITERATURE

6.1 Occlusive arterial disease - a systemic disease

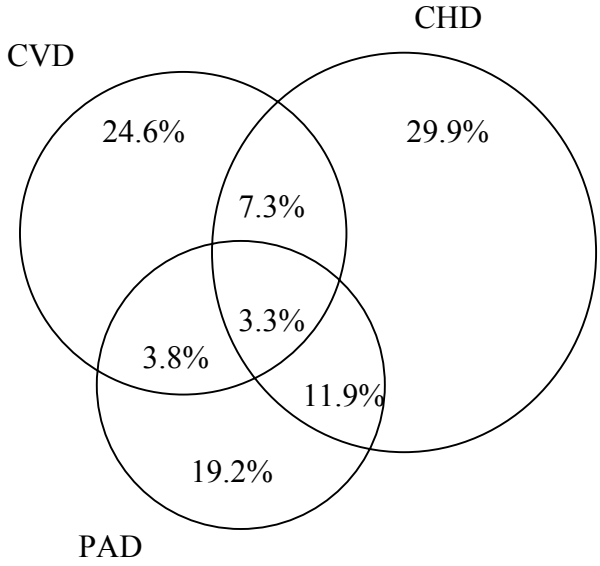
Atherothrombotic arterial disease is a systemic disease affecting, in principle, all of the arterial tree with the carotid-, coronary- and lower limb vessels being areas of predilection. Its distribution differs individually, but it can grossly be estimated that almost all patients presenting with symptoms of claudication or critical leg ischaemia do have manifestations of the disease elsewhere, and the disease surfacing as occlusive arterial disease of the lower limbs only reflects the state of the overall vasculature of the patient (Newman 1993).

The clinical manifestations of atherosclerosis in different organs have been reported to occur with different frequency. According to the Framingham Study coronary heart disease (CHD) showed symptoms in males 8 times as often as cerebrovascular disease and PAD twice as often. In females cerebrovascular disease and PAD occurred equally often and the incidence of coronary heart disease was fourfold that of PAD (Kannel 1970). More recent data by Aronow and Ahn emphasises a more even distribution with CHD occurring approximately twice as often as the other two manifestations (Aronow 1994). Similar proportions have been reported in the CAPRIE study, although CAPRIE data is skewed by the selection process of the study (CAPRIE steering group 1996, Dormandy 1999d). It can nevertheless be used to illustrate the overlap of different manifestations. (*Figure 1*).

Figure 1: Distribution of the three main manifestations of occlusive arterial disease



Aronow & Ahn 1994



CAPRIE 1996 as modified by Dormandy (Dormandy 1999d)

In addition to the different sites of manifestation the degree of atherosclerosis and its symptoms differs. The severity of the disease is of considerable importance as it influences treatment and prognosis. Therefore various classifications have been developed. In coronary heart disease several classifications have been developed, the most commonly used are the classification of the New York Heart Association (The Criteria Committee of the New York Heart Association 1964, Goldman 1981) and the Canadian Cardiovascular Society Grading Scale (Campeau 1976). These classifications grade the patients according to the experienced fatigue and angina pectoris symptoms in different degrees of exercise (*Table 1*).

Table 1:

The New York Heart Association Functional Classification of Coronary Heart Disease (NYHA-classification) and the Canadian Cardiovascular Society Grading Scale for Angina Pectoris (CCS classification):

	NYHA	CCS
Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation dyspnoea or anginal pain.	Ordinary physical activity does not cause angina: No angina occurs when walking or climbing stairs; angina does occur with strenuous or rapid or prolonged exertion at work or recreation
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.	Slight limitation of ordinary activity: when walking or climbing stairs rapidly; walking uphill; walking or stair-climbing after meals, in the cold, in the wind, under emotional stress, or only during the first few hours after awakening; walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.	Marked limitation of ordinary physical activity: Angina occurs when walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Inability to carry on any physical activity without discomfort: Anginal syndrome may be present at rest.

Similar to the NYHA-classification, the complications of atherosclerotic cerebrovascular disease can be classified according to severity. These have, however, very different ramifications compared to the stages in cardiovascular disease, as the course and prognosis are much less predictable. Three main stages of cerebral blood flow impairment can be distinguished. The most severe form is the irreversible brain infarction, with symptoms differing according to the site of infarction. In cases with prolonged ischaemic symptoms dissolving slowly within weeks, the term PRIND (prolonged reversible ischaemic neurological deficit) has been used, but largely abandoned today. The least severe symptom of cerebral blood flow impairment is the transient ischaemic attack (TIA) usually lasting only a few minutes, but often being a prodromal sign of an eventual brain infarction (Goldstein 2001, Straus 2002).

Altogether the varying degrees of the different manifestations can roughly be summarised as shown in *Table 2*, with coronary infarction being equivalent to permanent brain infarction and tissue loss in the leg, which could be understood as leg infarction.

Table 2: Comparison of the main symptomatology in the main manifestations of atherothrombotic disease

Coronary artery Disease	NYHA[§] II / NYHA III CCS [¤]II / CCS III	NYHA IV CCS IV	AMI*
Cerebrovascular disease	TIA[$]	PRIND[£]	Cerebral infarction
Peripheral vascular disease	Claudication	Rest pain	Ulcer/ Gangrene
Fontaine Classification	(Fontaine II)	(Fontaine III)	(Fontaine IV)
Rutherford Categories	1-3	4	5-6

[§] NYHA= New York Heart Association functional class, [¤]Canadian Cardiovascular Society Classification, *AMI= acute myocardial infarction, [$] TIA= transient ischaemic attack, [$]PRIND= prolonged reversible ischaemic neurologic deficit

As the disease is a systemic one and the severity of one manifestation reflects the state of the total vascular tree (Newman 1993b), it is clear that most of these patients are multimorbid. The other vascular manifestations of atherosclerosis have to be taken into account when planning the treatment of PAD (von Knorring 1995, Hertzer 1984). The existing coronary artery disease represents a major operative risk and reflects the high in-hospital cardiac mortality during and after surgery for PAD in general (Sprung 2000) and CLI in particular.

The general nature of the disease, apart from causing different manifestations of the disease, affects the survival of the patients with occlusive arterial disease. Patients suffering from claudication have a life expectancy about 10 years less than the general population (Boyd 1962, Bloor 1961). Accordingly, the

level of ankle brachial pressure indices (ABI) is reflected in the survival of the patients with increasing mortality rates proportional to declining ABIs (Jelnes 1986, Mc Dermott 1994, Howell 1989). Patients with an ankle brachial pressure index less than 0.9 have a significantly higher mortality than patients with an ABI above 0.9 (Newman 1993a, Vogt 1993, Leng 1996 b). The cause of death is reported as related to vascular causes in 53-80% percent of the patients with occlusive arterial disease (Jelnes 1986, Leng 1996, Davey Smith 1990, Bainton 1994). Intermittent claudication increased the risk for cardiovascular death with a relative risk of 2.67 (Leng 1996 a). CHD is reported to occur in persons with PAD 2.5 times as often as in persons without PAD (da Silva 1990). Hertzer et al showed that patients with PAD (either IC or CLI) had up to 90% coronary artery disease detectable by coronary angiography, and 57% of it was classified as advanced or severe (Hertzer 1984).

Seen from the reverse angle CHD is associated with 2.7 times the risk of developing IC than in the general population (Murabito 1997). IC is developed 2.3 times more often in persons with previous evidence of CHD than without CHD (da Silva 1990). In the presence of coronary artery disease PAD is reported in 33% of elderly patients (Aronow 1994). The prevalence of PAD in patients with coronary heart disease is in proportion with the severity of coronary lesions: In a study by Atmer 18% with mild coronary artery disease were found to have PAD, measured using pressure measurements and digital PVR, while 32% of those with marked coronary artery disease had detectable PAD (Atmer 1995).

Cerebrovascular disease (CVD) has been reported to exist in 15-57% of PAD-patients (Klop 1991, Aronow 1994, Alexandrova 1996). Asymptomatic cerebrovascular disease has been found to be three times as common as symptomatic CVD (Alexandrova 1996).

In obduction studies the atherosclerotic lesions seem to predominate in the proximal lower limbs, with Rutherford Dow discovering an involvement of 100% in the superficial femoral arteries and popliteal arteries, while coronary arteries showed an involvement of 75% and carotid arteries 58% (Rutherford Dow 1925). In a Finnish autopsy study the femoral artery was involved in 73%, coronary arteries in 83% and carotid arteries in 68% of the cases (Vankka 1967). These numbers are much higher than the prevalence of symptoms caused by atherosclerotic manifestations (*Figure 1*) (Aronow 1994). It can be speculated that coronary and cerebral circulation may be more vulnerable to atherothrombotic events than the lower limb circulation. Whether this is due to better collateral formation, slower progression of the disease, diameter of the vessel involved or differing tolerance for ischaemia of the various tissues, is unclear.

6.2 Etiology of Critical leg ischaemia

6.2.1 Pathophysiology of atherosclerosis and its peripheral manifestations

Atherosclerosis is a complex process with several etiologic factors influencing its progression. Not all etiologic factors are known, but some factors associated to atherosclerosis have been identified. It is not merely a degenerative process of the vessel wall, but is promoted by chronic inflammation and disturbing the function of the endothelium, an important factor in vascular autoregulation, growth and anticoagulation (Davies 1993). The initiation of an atherosclerotic lesion is a result of increased shear stress or endothelial damage, LDL migration into the intima and an inflammatory response to injury.

The endothelium is a layer of cells lining the inner surface of the vessel wall. It plays an important role in maintaining vascular tone by secretion of several compounds participating in vasodilation and vasoconstriction (Davies 1993). Prostanoids, nitric oxide and endothelium derived hyperpolarisation factors mediate a local vasodilation while endothelin and vascular angiotensin II produce a vasoconstriction (Davies 1993). Oxygen radicals inactivate nitric oxide and inhibit prostanoid synthesis, acting as vasoconstrictors. Other features of the endothelium include interactions with the coagulatory system, inflammatory response and regulation of vascular growth (Davies 1993). All these functions are affected by endothelial damage, being both the cause and result of atherosclerosis.

The increased shear stress existing in arterial branches and curvatures causes the architecture of the endothelium to change. The endothelial cells become polygonal in shape and do not have any particular orientation as opposed to the cells in linear flow environments, which are ellipsoid in shape and are aligned according to the direction of the blood flow (Lusis 2000). The junctions of the polygonal cells show an increased permeability, causing areas of increased shear stress to show a predisposition for atherosclerotic lesions (Lusis 2000).

Increased permeability or injury of the endothelial layer allows lipoprotein particles, predominantly LDL, to accumulate in the intima. LDL particles diffuse passively through the endothelial layer, especially when blood LDL-levels are elevated (Lusis 2000).

In the intima, native LDL undergoes minimal oxidisation through lipoxygenases. This minimally oxidised LDL is an inflammatory substance, which causes the endothelial cells to produce proinflammatory and adhesion molecules such as M-CSF (macrophage colony stimulating factor), selectins, and monocyte chemotactic protein. Monocytes will subsequently adhere to the endothelium and migrate across the endothelial layer into the intima. Once the monocytes have reached the intima, they will proliferate and differentiate into macrophages (Lusis 2000, Hiatt 2000).

The LDL is further modified by oxidisation, lipolysis, proteolysis and aggregation in which the mast cells located in the vessel wall seem to play an important role (Kovanen 1993). Myeloperoxidase, produced by endothelial cells and macrophages, causes oxidisation of the LDL-particles through highly reactive oxygen species. Secretory phospholipase promotes oxidisation while sphingomyelinase seems to mediate aggregation of LDL. The hereby-modified LDL inhibits the production of nitric oxide in the endothelial cells, hampering vascular autoregulation.

Unlike the native LDL, the modified LDL is readily taken up by macrophages via scavenger receptors. The macrophages become foam cells (Lusis 2000, Hiatt 2000), which accumulate in the intima forming fatty streaks (Kovanen 1993).

In the inflammatory process macrophages and T-lymphocytes secrete cytokines and growth factors, which promote smooth muscle cell migration from the media and their proliferation (Lusis 2000). The proliferation is further promoted by platelet-derived growth factor and angiotensin II produced by the renin angiotensin pathway (Lusis 2000). The migrated smooth muscle cells transform from “contractile” to “secretory” cells and secrete fibrous elements as the extracellular matrix (Hiatt 2000) thus producing a fibrous plaque. Occasionally even smooth muscle cells may become engorged with lipid and become foam cells as well (Hiatt 2000).

The fibrous plaque will grow by accumulating more lipids and cells and by producing more extracellular matrix. The growth is initially directed towards the adventitia and subsequently towards the lumen of the vessel (Lusis 2000). Through growth of the plaque the lumen of the vessel becomes stenosed and will occasionally occlude.

With the apoptosis of the foam cells, producing the necrotic core of the plaque, the fibrous plaque gains complexity (Hiatt 2000). Its necrotic core consists of lipids and cell debris. It is rich of tissue factor, an important trigger in the coagulation cascade, which is secreted by macrophages and endothelial cells activated by oxidised LDL (Lusis 2000). Advanced plaques may also contain haemorrhages and neovascularisation and finally vessel wall cells transforming into osteoblast-like cells. These secrete a matrix scaffold, that calcifies resembling bone formation and results in plaque calcification (Lusis 2000, Hiatt 2000).

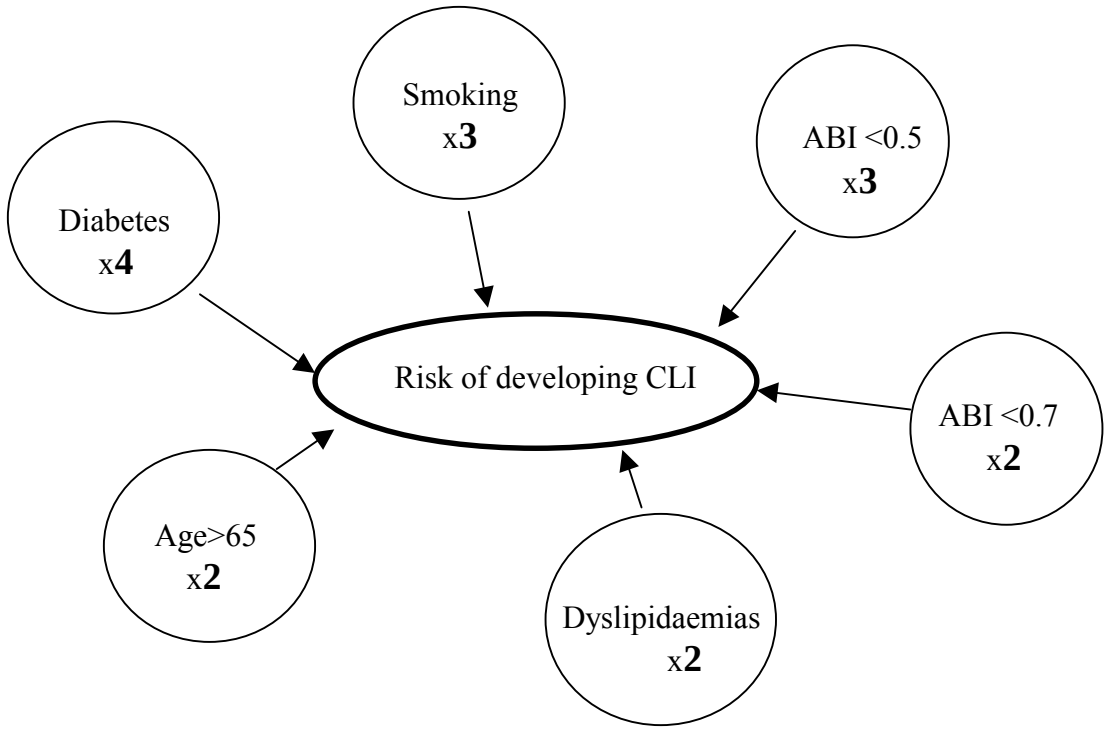
Acute ischaemic events such as acute myocardial infarction or “acute on chronic”-ischaemia are usually triggered by acute thrombosis caused by plaque rupture. Rupture usually occurs in plaques with thin fibrous caps and increased numbers of inflammatory cells (Lusis 2000). The inflammatory cells inhibit matrix production and produce proteases that degrade extracellular matrix (Lusis 2000). Thereby inflammation plays an important role in plaque rupture and subsequent thrombosis. In addition to the thrombogenic features of the atherosclerotic vessel wall, flow dynamics and the properties of the blood itself play a significant role in the development and course of the atherothrombotic disease.

Critical leg ischaemia may be caused by several mechanisms, the most important of which is atherosclerosis with superimposed thrombosis and resulting obstruction of the arterial inflow of the foot. Other possible mechanisms are diabetic microangiopathy (Tooke 1995, Ubbink 1993) and inflammatory diseases such as thromboangiitis obliterans (Olin 2000).

6.2.2 Risk factors for – and factors related to the progression of – occlusive arterial disease

The risk factors for general atherothrombotic diseases are associated with peripheral arterial disease. Different risk factors have different areas of predilection. Hypertension is one of the main risk factors for carotid artery disease and stroke (Cutler 1989), while the role of hypertension in the progression of the lower limb arterial disease is much less pronounced. Dyslipidaemia is accepted as a main risk factor for coronary heart disease, while its role in peripheral arterial disease is not yet established (Tasc 2000). In contrast to that, smoking is the main risk factor for lower limb arterial disease, especially of the proximal vessels (von Knorring 1992), while diabetes is the most important risk factor for distal PAD of the legs (Kannel 1979) and development of critical leg ischaemia (Dormandy 1999c) (*Figure 2*).

Figure 2: The influence of different risk factors on the progression of PAD with subsequent development of CLI (Dormandy 1999c)



6.2.2.1 Diabetes

6.2.2.1.1 Diabetes and atherosclerosis

Diabetes mellitus is one of the most important risk factors causing PAD and the most important etiologic factor in the development of CLI. It carries a 2-4-fold risk to develop PAD (Beckman 2002, Kannel 1979) with one third of the diabetics being affected (von Knorring 1992). A 5-fold risk to develop CLI (Fisher 1999), a 5-fold major amputation risk (Melliere 1999) and a 15 -24-fold risk to undergo any amputation (Eggers 1999) have been reported. The duration of diabetes correlates with the incidence of PAD (Beckman 2002) while in non-diabetic patients the incidence is strongly associated with age. Diabetes affects mostly the distal arteries of the lower extremities (Beckman 2002, Mc Millan 1997, Chantelau 1984) and is in the first place regarded as a macrovascular disease (LoGerfo 1984). At least a third of all CLI patients are reported to be diabetic (Bailey 2003, The Vascular Surgical Society of Great Britain and Ireland 1995). Even up to 55% of critically ischaemic patients in surgical series have been reported to be diabetics (Luther 1994)

Atherosclerosis is the main complication in diabetes. Like the risk of developing PAD, the risk for both stroke and coronary heart disease is 1,5-4-fold in all age groups together (Beckman 2002, Pell 1970). In the younger age group the stroke risk is reported to be about 10-fold (Beckman 2002). The prevalence of silent myocardial ischaemia is reported to be 10% in insulin dependent diabetics and 8% in non-insulin

dependent diabetics (Koistinen 1990). It is estimated to occur 2-3 times as often in diabetics than in non-diabetics (Koistinen 1990), which as such is prone to cause difficulties in identifying and treating diabetic patients with CHD in time.

6.2.2.1.2 Mechanisms contributing to the development of PAD and CLI in diabetics

In diabetes, PAD and CLI, as well as other manifestations of atherothrombotic disease such as CHD, are caused by several mechanisms: vascular autoregulation is impaired, atherogenesis is enhanced by leukocyte migration and coagulation is increased. Furthermore, diabetes causes large artery stiffness with peripheral flow reduction (Suzuki 2001) and ensuing mediasclerosis.

Hyperglycaemia impairs nitric oxide-mediated vasodilation by blocking the endothelial nitric oxide synthase (eNOS). Hyperglycaemia as well as insulin resistance increase the production of reactive oxygen species, which also inhibit nitric oxide synthesis and decrease the synthesis of vasodilatory and antiplatelet prostanoids (Beckman 2002). Furthermore, diabetes increases the production of vasoconstricting substances, especially endothelin, which causes vasoconstriction, renal salt and water retention, activation of the renin-angiotensin system and vascular smooth muscle hypertrophy. Other vasoconstricting substances increased by diabetes are vasoconstrictor prostanoids and angiotensin II (Beckman 2002). Vascular autoregulation is severely impaired by this, but systemic blood pressure may be elevated as well.

In addition to vascular autoregulatory impairment, diabetes participates directly in atherogenesis by facilitating T-cell lymphocyte and monocyte migration into the intima. Proinflammatory mediators and the expression of leukocyte adhesion molecules on the endothelial surface are enhanced by hyperglycaemia induced increase of oxidative stress and advanced glycation end-products (AGE). The resulting migration of leukocytes into the intima leads to fatty streak- and atheroma-formation (Beckman 2002). This is even enhanced by lipid abnormalities, which are often coexisting in diabetic patients.

6.2.2.1.3 Diabetes and mediasclerosis

Diabetes is an important and common cause for mediasclerosis (Goss 1989, Chantelau 1984, Lepäntalo 2003) causing pseudohypertensive pressure values through incompressible arteries, and thereby hampering the basic assessment of PAD- patients (Laing 1998). Arterial wall stiffness has been seen to correlate with PAD symptoms, but not with pressure values (Taniwaki 2001). This is understandable, as stiffening of the arteries and mediasclerosis is prone to distort the measured pressure values.

Mediasclerosis is most often affecting the larger arteries and predominantly the lower limb, but there is evidence that mediasclerosis may affect brachial arteries as well (Edmonds 1982). Especially in patients with diabetic neuropathy even the small arteries in the digits and toes are not always spared (Young 1993). The involvement of digital arteries is, however, rare and toe pressures can still be used as alternative to ankle pressures in patients with pseudohypertensive ankle pressures (Young 1993). Early mediasclerosis is seen to occur already in childhood as an elasticity reduction of the large arteries (Pillsbury 1974, Mc Millan 1997). Arterial tissue damage in diabetes is thought to be directly mediated through advanced glycation end-products (AGE) such as HBA_1 (Mc Millan 1997, Yki-Järvinen 2000). The ageing of the arterial collagen fibres is accelerated through production of matrix metalloproteinases

(Beckman 2002) and elastin formation is slowed down by hyperglycaemia (Mc Millan 1997) resulting in arterial wall stiffening. Later, the walls of elastic arteries thicken and eventually calcify, contributing further to the stiffening of the arterial wall. The thickening of the basement membrane in diabetics has been seen not to inhibit oxygen diffusion but to change the anatomy of the vessel (LoGerfo 1992)

6.2.2.1.4 Diabetes and atherosclerotic plaque formation

The hampering of collagen production and accelerated ageing of collagen fibers causes, apart from arterial wall stiffness, also plaque instability (Beckman 2002). It has been observed that in diabetics the advanced atherosclerotic plaques have less smooth muscle cells than in controls (Beckman 2002). Smooth muscle cells are supposed to produce collagen fibres to stabilise the plaque. Diabetes seems to promote plaque instability by inhibiting smooth muscle cell migration and increasing smooth muscle cell apoptosis (Beckman 2002). In addition to plaque instability in diabetes, the production of tissue factor, a major procoagulant, is enhanced and the level of factor VII is increased, while the level of endogenous anticoagulants such as antithrombin III and protein C are decreased (Beckman 2002). Furthermore, intrinsic platelet activating features are enhanced, while platelet stabilising features are diminished in diabetes (Beckman 2002). As a result, diabetic patients are particularly prone to develop thrombi and have impaired fibrinolysis.

6.2.2.1.5 Other complications of diabetes

Other complications of diabetes such as diabetic neuropathy, diabetic retinopathy and diabetic nephropathy may contribute to the development and progression of PAD in diabetic patients.

Diabetic sensory neuropathy, which in vascular surgical patients is often not sufficiently investigated, masks pain as a warning signal and is partly responsible for many small injuries occurring in daily life (Mc Millan 1997, Pecoraro 1990, Laing 1996). These injuries may lead to neuroischaemic ulcers, if nutritional flow is inadequate to support the inflammatory reaction necessary for wound healing. Due to neuropathy these injuries and following ulcers often stay painless and the patient is frequently unaware of their existence (Laing 1998) which, due to lacking treatment, may deteriorate the situation even further. Additionally the neuropathy itself constitutes an independent risk factor for the development of ulcers and thereby for the amputation risk (Adler 1999). Apart from sensory neuropathy Diabetes also causes autonomic neuropathy (Laing 1998), which leads to impairment of the cardiac response (Hornung 1989), affects gastric and enteral motility and disturbs the vascular regulatory function, especially reflectory vasoconstriction (Mc Millan 1997, Takahashi 1998). Loss of reflectory vasoconstriction can produce orthostatic hypotension, as well as direct damage to the endothelium in the lower extremity through elevated intra-arterial pressures in the foot (Tooke 1995). This is thought to be the mechanism behind the unusually distal localisation of the atherosclerotic lesions in diabetic patients (Mc Millan 1997). Another feature in diabetic autonomic neuropathy is the opening of small peripheral arteriovenous shunts - an ”autosympathectomy” - which, although increasing the overall blood flow in the periphery, in fact decreases the nutritive blood flow to the tissue (LoGerfo 1992, Laing 1998, Takahashi 1998, Lepäntalo 2000).

Diabetic retinopathy frequently deteriorates the eyesight of the patient through microaneurysm and microvessel loop formation, haemorrhage and macular oedema (Mc Millan 1997). The loss of eyesight

is prone to increase the risk of injuries in the legs, which may – in conjunction with impaired blood supply – lead to critical leg ischaemia.

Diabetes may cause renal insufficiency through thickening of the glomerular basement membrane and collagen and high carbohydrate connective tissue deposition (Mc Millan 1997). It may lead to renal failure and eventually to dialysis, additionally promoting the process of atherosclerosis.

6.2.2.1.6 Diabetes in combination with other risk factors

Smoking in conjunction with diabetes increases the levels of leukocyte adhesion molecules more than in non-diabetics, thus further promoting the development of intimal inflammation and atherogenesis (Takeuchi 2002).

Adult type diabetes often coexists with dyslipidaemia (McMillan 1997) and hypertension, together referred to as the metabolic syndrome with predominance for vascular complications (Isomaa 2001).

6.2.2.1.7 Treatment of diabetic vascular manifestations

Although diabetes affects vascular function on every level, therapy may reduce the complication rate: Insulin therapy in type II diabetics has been observed to improve vascular function (Vehkavaara 2000), and intensive treatment has been observed to delay the development of complications and lower the complication rate of type I diabetes (Reichard 1993, The Diabetes Control and Complications Trial Research Group 1993).

Revascularisation procedures have been seen to succeed equally to procedures performed in non-diabetic patients (LoGerfo1992). Even microcirculation has been observed to improve to a certain degree after successful revascularisation (Arora 2002).

6.2.2.1.8 Diabetic microcirculatory disease

The evidence concerning microcirculatory changes in diabetics seems somewhat contradictory. It has been generally accepted that microvascular lesions play a great role in the development of late vascular diabetic complications (Tooke 1995). Conrad, however, found no difference in the number of small vessel occlusions between diabetics and non-diabetics when examining amputated legs using casts of the vasculature (Conrad 1967). Irwin even reported no difference in vascular blood flows between patients with and without small vessel disease (Irwin 1988, LoGerfo 1992). Despite the absence of great anatomical changes, the function of the microvasculature may be compromised with subdued autoregulation. Diabetes is characterised by increased microvascular flow in peripheral tissues (Tooke 1995) resulting from loss of autoregulation. The increased flow and increased pressure (Sandemann 1992) results in increased shear stress in the vessels (Tooke 1995). The growing shear stress causes tissue injury through increased permeability of the endothelium. With ongoing tissue injury, basement membrane thickening and arteriolar hyalinisation develops, further interfering with microvascular autoregulation (Tooke 1995). Additionally to the direct effects of microvascular disease on nutritive

flow, some evidence suggests that it may participate in the development of diabetic neuropathy, which initially seems to be an ischaemic disease (Tesfaye 1994).

Poor glycaemic control has been reported to compromise microcirculatory velocities (Jörneskog 1998), while diabetes itself has been seen to increase microvascular blood flow (Ubbink 1993). In some of the diabetic patients, capillary density seems to be lower (Ubbink 1993) than in non-diabetics, suggesting that although anatomical changes are not present in all diabetic patients, they may be a significant feature in a subgroup.

6.2.2.2 Other risk factors

6.2.2.2.1 Smoking

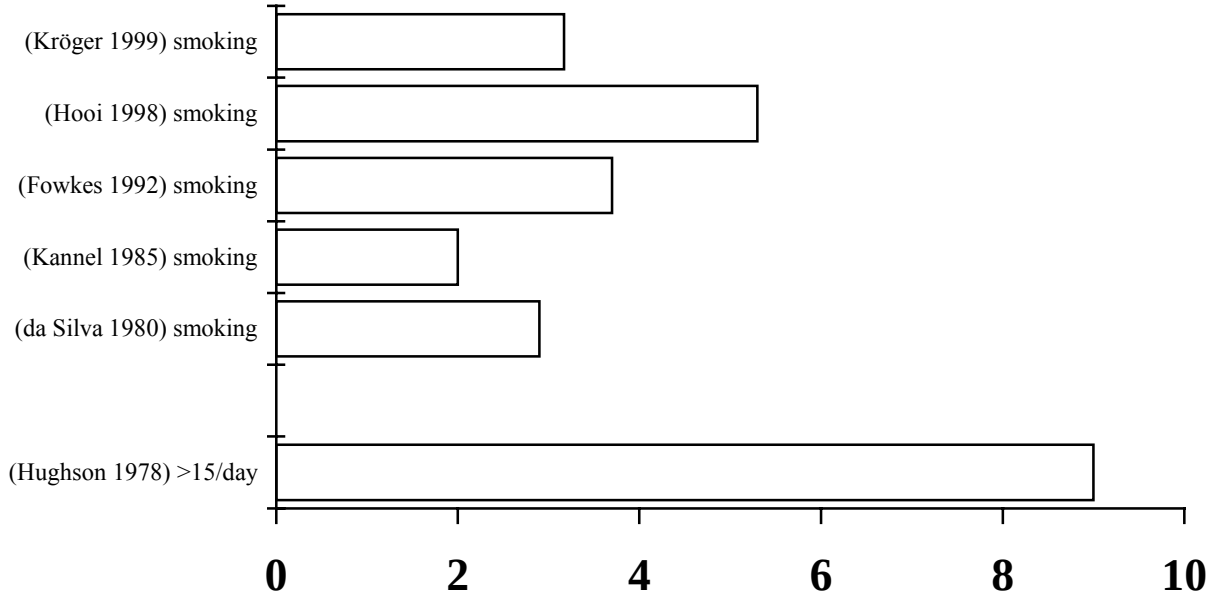
Major adverse effects of cigarette smoking have been known for decades, and new evidence on the adverse effects continues to be published. The association of tobacco smoking and claudication symptoms has been reported as early as 1911 (Erb 1911). Still, in spite of recurring government campaigns against smoking, as well as restrictions and taxes imposed on the selling of tobacco products, the smoking of tobacco continues to be a major health problem in the Western World and a growing problem in developing countries. Educational campaigns have, however, been shown to reduce smoking in Finland (Leppo 2003). At the same time the cardiovascular mortality has markedly decreased in Finland (Favilli 1998, Jousilahti 2003). Despite the widely spread knowledge of the adverse effects of the use of tobacco products, smoking cessation rates are still very low and patients do not receive enough support (Cassar 2003, Hobbs 2003).

Tobacco smoke contains nicotine that mediates vasoconstriction and causes a strong addiction, as well as carbon monoxide, which causes hypoxia. A further variety of different substances are also contained in tobacco smoke, some of which may damage the vasculature through induction of oxidative stress and subsequent endothelial damage (Glasser 1996), while others are carcinogenic or are affecting the coagulation system (Lassila 1989). Tobacco smoking is also believed to facilitate the migration of leukocytes into the intima by increasing the level of circulating adhesion molecules, which has been observed both in non-diabetic and especially in diabetic subjects (Ridker 1998, Takeuchi 2002). In this manner smoking may directly promote inflammation, plaque formation and thrombosis.

Tobacco smoking is the strongest risk factor for peripheral occlusive arterial disease (Fielding 1985, von Knorring 1992), which has been confirmed in several epidemiological studies (Murabito 1997, Bainton 1994, Meijer 1998, Fowkes 1992). Smoking is reported to double or almost triple the risk to develop atherosclerosis, with the risk increasing with advancing age (Kannel 1985, da Silva 1990, TASC). The risk is dose dependent and increases with the number of cigarettes smoked per day (Fielding 1985, Lassila 1988). It is, however, noteworthy that occasional smokers also have an increased risk for atherosclerosis in comparison to non-smokers (da Silva 1990, TASC). In contrast to diabetes, the distribution of arterial lesions caused by smoking is more concentrated on the larger vessels (Vogt 1992) although an independent association between smoking and stroke has been observed (Shinton 1989, Wolf 1988). Interestingly, tobacco smoking seems to be more strongly associated with PAD than to coronary heart disease (Heliövaara 1978, Fowkes 1992, Lepäntalo 1991). In comparison to non-smokers

the development of symptomatic intermittent claudication is reported to be as high as 9-fold in all smokers (Hughson 1978a), with the risk being 15-fold in men and 7-fold in women (Hughson 1978a).

Figure 3: Relative risk of developing PAD when smoking (compared to non-smokers).



Disease progression to rest pain and critical leg ischaemia is strongly associated with continued smoking (Jonason 1986, Quick 1982). Ankle pressures have been shown to decline in persistent smokers compared to the patient group having given up smoking (Quick 1982, Jonason 1986). Even a correlation between smoking and amputation for ischaemia has been reported (Liedberg 1983).

Claudication itself is associated with a reduced life expectancy, but even among claudicants smoking is associated with an increased mortality (Reunanen 1982). Accordingly, smoking cessation has been reported to improve the prognosis of claudicants (Hughson 1978b) with reduced mortality (Jonason 1987, Fielding 1985), lowering of amputation rates (Juergens 1960), improved graft patency (Smith 1996), improved walking distance (Quick 1982), improved ankle pressures (Quick 1982) and improved symptoms (von Knorring 1992).

Additionally to being atherogenic itself, tobacco consumption has a synergistic effect in combination with other risk factors (Fielding 1985, Lassila 1989). In the Edinburgh artery study tobacco smoking increased the risk for PAD significantly in diabetic subjects (MacGregor 1999). Elevated non-HDL cholesterol also had a greater influence on ABI pressure values in current smokers than in ex- and non-smokers (Fowkes 1992).

Smoking is strongly associated with thromboangiitis obliterans (or Bürger's disease) that involves mainly small and medium sized vessels of the limbs. Although the aetiology itself is not known, tobacco consumption seems to play an important role in the development and persistence of the inflammatory and thrombotic process of Bürger's disease (Olin 2000). Unlike atherosclerosis, Bürger's disease involves both arteries and veins and is characterised with marked cellular proliferation and inflammatory

infiltrate in the thrombus (Olin 2000). Bürger's disease occurs predominantly in young smoking men, but the number of elderly women affected is increasing of late. It causes peripheral claudication and peripheral trophic lesions and may therefore be mistaken for atherosclerosis. It even may coexist with atherosclerosis making a distinction more difficult and may aggravate its course (Olin 2000). The main therapeutic measure is complete abstinence of tobacco products – without it all other forms of therapy can be regarded as palliative (Olin 2000).

Tobacco consumption is also the main reason causing chronic obstructive pulmonary disease as well as emphysema (Fielding 1985), lowering the pulmonary capacity and thereby additionally affecting the oxygen supply of blood and tissue. Another common complication of smoking is coronary heart disease, which together with a compromised pulmonary function poses an additional risk factor for perioperative complications.

6.2.2.2.2 Hypertension

The association between hypertension and PAD has been observed in several epidemiological studies (Kannel 1985, Murabito 1997, da Silva 1990, Bainton 1994, Meijer 1998, Beach 1980), while in other studies no association could be detected (Reunanen 1982, Davey Smith 1990). It may be speculated that these differing results were influenced by factors like different age of the population studied, use of only systolic pressure, or the method by which PAD has been identified. Arterial hypertension is not a single feature but has different implications in different age groups. In a younger age group it is generally accepted that elevation of the diastolic blood pressure poses a risk to the arterial vasculature as well as to the heart itself (Cutler 1989, MacMahon 1989). In elderly patients, however, the stiffening of the arteries and isolated systolic hypertension seems to play a greater role in terms of cardiovascular risk (Donnelly 2002). Therefore, more emphasis is to be directed to isolated elevation of systolic blood pressure (Stokes 1989, MacGregor 1999) and ensuing high pulse pressure.

The localisation of arterial lesions caused by long lasting hypertension differs somewhat from the distribution of lesions seen in diabetes. Hypertension damages the whole arterial tree with an emphasis on the heart, the carotid and cranial arteries (Cutler 1989, Stokes 1989) as well as renal arteries (Whelton 1989). Thus the relative importance of hypertension as a risk factor for PAD and its progression to CLI is not of the same magnitude as for CHD and especially for CVD.

The risk to develop PAD increases proportional to the systolic pressure level (Kannel 1985). A diastolic pressure above 95mmHg in men and 85mmHg in women is also associated with an increased risk to develop PAD (Kannel 1985). Similarly, in a Danish study on 60-year-old subjects, elevated systolic or diastolic pressures are both associated with an increased risk for PAD (Schroll 1981)

Hypertension is frequently associated with insulin resistance, hyperinsulinaemia, non-insulin dependent diabetes, obesity, abnormalities in fibrinolysis and dyslipidaemia, especially with small density LDL particles together comprising an entity called "metabolic syndrome" (Reaven 1988, TASC 2000). All of these risk factors are independently being associated with an increased risk for general atherosclerosis (Grundy 2004). Peripheral vascular disease has been associated with metabolic syndrome (Costa 2004). Metabolic syndrome has been found to correlate with a higher rate of coronary heart disease and smaller LDL size (Isomaa 2001). In metabolic syndrome neuropathy seems to be related to small dense LDL-particles (Isomaa 2001).

6.2.2.2.3 Thrombophilia

Thrombophilia has been increasingly associated with the development and progression of PAD (Burns 2001). In young PAD-patients as many as 76% have a hypercoagulable state (Burns 2001). Activated protein C (APC)-resistance is mostly caused by a mutation in Factor V, which makes it more resistant to activated protein C. Also pregnancy, contraceptive pills and antiphospholipid antibodies are known to cause APC-resistance. It has been found to occur disproportionately often in patients with PAD (Burns 2001). Among those who have APC-resistance, graft occlusion occurs more often than in other patients with bypass reconstructions (Ouriel 1996). Hyperfibrinogenaemia is present in 50% of patients with PAD (Burns2001). Plasma fibrinogen levels have been found to correlate with mortality in stable claudicants and may be used as a prognostic factor when assessing both claudiation patients as well as critically ischaemic patients (Banerjee 1992, Doweik 2003). Hyperhomocysteinaemia has been found to be associated with PAD (Mohan 1999a), it is suggested to influence endothelial function and platelet activation and thus to promote PAD progression (Mohan 1999 b). It has even been speculated that homocysteine may be a factor participating in the development of myointimal hyperplasia (Hansrani 2002). Its role as an independent risk factor is, however, still controversial (Pasterkamp 2002) and there are suggestions that it may be more the result of, rather than the cause for advanced atherosclerosis and reflecting renal function to some extent (Brattstrom 2000).

6.2.2.2.4 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 2002). In future the evidence on long-term effects and the effect of treatment on peripheral vascular diseases will increase and assessment of blood lipoprotein levels may most probably become routine in vascular surgical patients. The evidence of an existing association between blood lipoprotein levels and the development of PAD has been inconclusive (Vogt 1992). In some studies, elevated blood cholesterol levels are a clear risk factor (Kannel 1985, Schroll 1981), while in others an association could not be found (Hughson 1978a). Low HDL with elevated LDL as well as elevated triglyceride and lipoprotein levels have been shown to be associated with occlusive arterial disease and its progression (da Silva 1990, Bainton 1994, Fowkes 1992, Smith 1996, Greenhalgh 1971, Dionyssiou-Asteriou 2000).

The imbalance of lipoproteins plays a role in developing endothelial dysfunction. The endothelial damage caused by oxidised LDL and triglyderides maintains an inflammatory process in the endothelium and inhibiting nitric oxide production, hampering the vasodilator function of the endothelium (Glasser 1996, Laws 2004). When LDL and/or triglyceride excess is persisting, the lipoproteins start to migrate into the endothelium causing an inflammatory process resulting in the eventual calcification of the plaques in the vessel wall. The more dense particles of LDL are known to be more atherogenic (Glasser 1996).

Statins are, for the time being, the most frequently used antihyperlipidaemic drugs. They lower LDL levels through inhibiting HMG CoA reductase activity in the liver. They also calm down the inflammatory process by inhibiting the expression of pro-inflammatory cytokines (Laws 2004) and thereby restore endothelial function. Statins also increase plaque stability by inhibiting LDL oxidation, lipid accumulation, macrophage infiltration as well as matrix metalloproetinase expression, increasing the collagen content of atherosclerotic plaques (Laws 2004). Dyslipidaemia is associated with

hypercoagulability and increased platelet activity (Opper 1995). Statins decrease platelet activity and improve the fibrinolytic response, also affecting coagulation (Laws 2004).

Some short-term evidence suggests that atorvastatin-treatment reduces intima-media-thickness in the carotid and femoral arteries (Youssef 2002), which may indicate that the lipid-controlling and anti-inflammatory effect of statin treatment may contribute to the stabilisation and regression of atherosclerotic plaques even in the lower extremities. The primary and secondary preventive effect of statins and other lipid lowering drugs in coronary heart disease has been established (Scandinavian Simvastatin Survival Study Group 1994, Salonen 1995, Lipid Research Clinics Program 1984) There is, however, evidence that by treating hyperlipidaemia the progression of the atherosclerotic process may be slowed down or reversed even in the lower limbs (Duffield 1983, Blankenhorn 1991, Pedersen 1998, de Groot 1995, Olsson 1990).

Other drugs used for lipid lowering purposes are fibrates inhibiting the HMG CoA reductase activity, activating a lipoproteinlipase-enzyme in the liver, muscles and the adipose tissue and thereby increasing the reduction of VLDL and LDL. Drugs of the cholestyramine-type inhibit the absorption of bile acids and reduce LDL levels.

6.2.2.2.5 Renal insufficiency

Apart from calcification of the viscera, impairment of renal function causes calcification of the arteries, partially through disturbances of the calcium and phosphorus metabolism (Parfitt 1969). Calcification of the arteries in renal insufficiency occurs predominantly in the media of the artery (Parfitt 1969), which makes renal insufficiency (Mäkisalo 1998, Leskinen 2002), together with diabetes and long lasting systemic corticosteroid treatment, one of the main reasons for mediasclerosis. Arterial calcification in uraemia usually begins either at ankle level or in the palmar and plantar arches (Parfitt 1969). The distribution of the calcification is more diffuse than in atherosclerotic plaques. In the early stages of mediasclerosis no narrowing of the arterial lumen is present but in advanced stages this may be the case (Parfitt 1969). The medial calcification impairs the elasticity of the artery as well as its regulatory function (Parfitt 1969), which may cause symptoms during exercise.

Apart from soft tissue calcification with mediasclerosis, vitamin D-related sclerosis of the intima may participate in the development of PAD in uraemic patients (Parfitt 1969). PAD is a major source of morbidity and mortality (Cheung 2000) in uraemic patients, with a reported prevalence of 22% in predialysis patients, and 31% in dialysis patients (Leskinen 2002). Patients with renal transplantation had a markedly lower prevalence of PAD (15%) (Leskinen 2002). Accordingly, amputation and survival rates also have been observed to be more favourable in patients with functioning renal transplants compared to dialysis patients (Eggers 1999). As diabetes is a frequent cause for renal insufficiency (Eggers 1999), a major proportion of uraemic patients suffer both from complications related to uraemia as well as diabetes (Eggers 1999). For diabetic patients, nephropathy constitutes an additional threat in terms of lower limb complications. Hill et al observed a 25% rate of foot problems among diabetic patients with end-stage renal disease, while diabetics without renal complications has a 10% rate of foot problems (Hill 1996). This may reflect an additional worsening of the vascular status and progression to CLI, once renal insufficiency has developed, or the renal involvement may simply be an indicator for advanced complications of diabetes as the underlying disease. Amputation rates among uraemics have analogously been observed to correlate with the presence or absence of diabetes (Eggers 1999).

Patients with renal insufficiency undergoing vascular surgery for critical leg ischaemia are reported to have an acceptable leg salvage (Peltonen 1998, Albers 2001), but a worse prognosis in terms of survival than other critically ischaemic patients (Biancari 2002, Eggers 1999, Taylor 1991, Kimura 2003). Especially patients with a manifestation of coronary heart disease in combination with critical leg ischaemia and uraemia have a poor outcome (Biancari 2002).

6.2.2.2.6 Neuropathy

Diabetic neuropathy has been found an independent risk factor for the development of ulcers (Adler 1999). Neuropathy contributes to lower limb problems playing a role in the development of ischaemic lesions. It may alter foot architecture causing callosities to form with a subsequent risk of developing neuropathic ulcers. Neuropathy, irrespective of its origin, also increases the risk for small injuries, which can cause neuroischaemic ulcers in the presence of PAD. Peripheral neuropathy can be caused by various factors such as diabetes, nephropathy, neurotoxic drugs (Argov 1979), vitamin deficiencies and alcohol consumption, with diabetes being the most important cause in vascular surgical patients. Neuropathy has been shown to be associated with a worse outcome in diabetic patients (Adler 1999), possibly reflecting the advanced stage of vascular and neurologic complications produced by diabetes. In fact, advanced neuropathy has been found to be an ischaemic process (Newrick 1986), while early neuropathy is suspected to be mainly of metabolic origin and evolving similar to other types of neuropathy (Myers1986, Mc Millan 1997).

6.2.2.2.7 Other risk factors

6.2.2.2.7.1 Obesity

Obesity is often associated with an unfavourable lipid profile, arterial hypertension and type 2 diabetes, which are all independent risk factors for PAD. Weight reduction is an essential part in the therapy of these diseases. Weight reduction improves glucose tolerance and lowers the blood pressure. However, most studies have failed to show obesity to be an independent risk factor for PAD. (Beach 1980, Schroll 1981, Reunanen 1982, da Silva 1980). This might be explained partly by the weight reducing effect of tobacco smoking (Fielding 1985). In epidemiological studies some of the normal weight may in fact have a clearly increased risk for developing PAD because of tobacco smoking, thus producing a confounding effect when assessing the correlation between weight and PAD.

6.2.2.2.7.2 Gender

Females are reported to develop PAD later in life than males (Kannel 1985) with an overall male/female ratio of 1.27 (Criqui 1985). Males are twice as likely to develop IC (Murabito1997, Kröger 1999, Beach 1980). The female advantage disappears after menopause (Kröger 1999). Female gender combined with diabetes has been observed to be associated with an adverse outcome of revascularsiation procedures (Luther 1997b, AhChong 2002). Smoking is reported to diminish or eliminate the advantage of female sex (Kannel 1985). The same phenomenon has been observed in diabetes in the development of atherosclerosis and intermittent claudication (Mc Millan 1997, Kannel 1985).

6.2.2.2.7.3 Age

Age as such is strongly associated with atherosclerosis and PAD (Roberts 1959, Schilling 1974, Vogt 1992). The incidence and prevalence of PAD increases sharply with age (da Silva 1990, Bainton 1994, Kannel 1985, Meijer 1998). Age is also associated with the progression of PAD to CLI (Murabito 1997, Reunanen 1982, Dormandy 1999c) as well as leg salvage and survival (Zdanovski 1998).

6.2.2.2.7.4 Physical inactivity

Engström et al assessed the presence of PAD in men without evidence of claudication symptoms in the Rose questionnaire, using ABI measurements and <0.9 as a cut-off point. They observed an association between physical inactivity and a higher prevalence of PAD (Engström 2001). Some connection between physical exercise and endothelial vasodilatory function also has been observed (Glasser 1996). Exercise is thought to alter the shear stress of the arterial wall in an oscillatory fashion, producing a beneficial effect in terms of PAD development (Shearman 1999). Exercise additionally improves cardiorespiratory status and results in positive changes to the lipid profiles (Tan 2000), which may contribute to the favourable effect of physical training.

6.2.2.2.7.5 Infectious factors

An association between chlamydia pneumoniae and coronary heart disease has been demonstrated (Leinonen 2002). Similarly the progression of PAD in the lower limbs seems to be associated with a chlamydia pneumoniae-infection (Lindholt 1999a), although the importance of this finding is not yet understood (Lindholt 1999b). An infection leads to microthrombus formation and thereby worsens the ischaemia by causing tissue necrosis (Lepäntalo 2000). In diabetic patients an ulcer has been seen to be associated with a higher C-reactive protein (CRP) level as a general inflammation marker (Upchurch 1997). The CRP-level as such has been observed to be associated with postoperative outcome of bypass surgery for CLI (Biancari 1999, Mätzke 2001).

6.3 Manifestations of lower limb arterial disease

6.3.1 Classifications of occlusive arterial disease

The first classification of occlusive arterial disease, still being in use, is the Fontaine classification, in which the severity of the disease is divided into four main categories (*Table 2*). It is solely based on symptomatic evidence, as are Rutherford's categories, which distinguish between minor tissue loss and major tissue loss as well as between mild, moderate and severe claudication (Ad Hoc Committee 1986) (*Table 2*).

6.3.2 Asymptomatic occlusive arterial disease

The occurrence of asymptomatic occlusive arterial disease is difficult to assess on population basis, as an assessment requires individual pressure measurements at the least. Most of the large population-based studies used only a questionnaire: the Framingham study, the Whitehall study, the Speedwell study and the Finnish prevalence study (Kannel 1985, Murabito 1997, Davey Smith 1990, Bainton 1994, Reunanen 1982). In these studies it is not possible to assess the occurrence of asymptomatic PAD, so only the ”tip of the iceberg” i.e. the symptomatic PAD is included into the prevalence numbers. Some studies have applied non-invasive measurement techniques: the Basle Study, the Edinburgh Study, a Danish study and the Rotterdam Study (da Silva 1980, Fowkes 1991, Schroll 1981, Meijer 1998). In the Basle Study angiographies were performed in addition to non-invasive haemodynamic assessment (oscillometry). In the Edinburgh study ankle brachial indices and reactive hyperaemia tests were used while the Danish study and the Rotterdam study relied on ankle brachial indices (Fowkes 1991, Schroll 1981, Meijer 1998). The proportion of asymptomatic PAD ranges in these studies between 4 and 11-fold compared to symptomatic claudication (*Table 3*).

Table 3: Proportion of asymptomatic PAD in relation intermittent claudication

Author	Method of assessment	proportion of asymptomatic PAD in relation to IC
da Silva 1980	A *+O[#]	7,4 : 1
Fowkes 1991	ABI[¤] +RH[&£]	5,5 : 1
Schroll 1981	AAR[$] <90%	4,3 : 1
Meijer 1998	ABI[¤] <0.9	10,9 : 1

*=angiographies
[#]=oscillometry
[¤]=ankle brachial indices
[&]=reactive hyperaemia
[£]=ankle brachial index <0.9 or reactive hyperaemia pressure drop >20%
[$]=ankle/arm ratio

The relation in these four studies is in the same order of magnitude except for the Rotterdam Study. The absence of symptoms in asymptomatic occlusive arterial disease can mostly be explained by the missing discrepancy between blood supply and demand. This may be the cause for the high prevalence numbers of asymptomatic PAD in the Rotterdam study, where inhabitants aged 55-85 or older were assessed, some of which lived in nursing homes and were likely to move around very little (Meijer 1998). The slightly greater proportion of asymptomatic PAD in the Basle study, in comparison to the Danish and the Edinburgh study, may result from the fact that angiography is a morphological assessment method not being able to distinguish between haemodynamically significant and insignificant narrowing of the arteries. It could be argued that the Basle study is thus slightly prone to overestimate the prevalence of significant asymptomatic PAD.

6.3.3 Intermittent claudication

Ischaemic pain occurring during exercise and dissipating swiftly during rest is called claudication, which in Latin means “limping”. The patient may alter his/her gait and start to walk asymmetrically after the onset of claudication pain, as he/she is thereby trying to decrease the amount of exercise performed by the painful muscle group. More importantly, the patient has to stop and rest every now and then, which makes the ambulation intermittent.

Intermittent claudication presents itself as pain, weakness or numbness in the muscle group distal to the diseased arterial segment. The symptoms are caused by accumulation of lactic acid as a product of anaerobic metabolism, resulting from an imbalance between oxygen demand and supply during exercise, when blood flow through the stenosed arterial tree or via a collateral network, is not sufficient. The patient is forced to rest and the diminished need for increased blood flow restores the oxygen levels in the muscle and the pain dissipates. Thus sufficient exercise is needed for the appearance of claudication pain. A sedentary patient not moving around for whatever reason may have lesions severe enough to cause symptoms of claudication without experiencing any significant pain.

Ischaemic claudication may be difficult to distinguish from other disorders causing similar symptoms (Fasih 2003). Spinal stenosis may cause similar pain that resolves after rest (Fasih 2003). Arthrosis of the joints and rheumatic diseases may cause pain during exercise, although the pain is often present at rest too. Neurological disorders such as neuropathies may cause pain, weakness and numbness in the legs. Deep venous obstruction and chronic compartment syndrome may also cause claudication pain but typically need more time to resolve than ischaemic claudication pain. (TASC 2000).

In the assessment of intermittent claudication, non-invasive methods, such as ankle pressure measurements at rest and after exercise or in a reactive hyperaemia test, should be used. Patients may have typical ischaemic pain during exercise without having haemodynamical evidence of insufficient blood flow at rest. This is well demonstrated in the Rotterdam study, where of 106 individuals with claudication according to the Rose criteria 33 had an ABI above 0.9 (Meijer 1998).

The prevalence and incidence of intermittent claudication has been addressed in several epidemiologic studies (Fowkes 1991, Bainton 1994, da Silva 1990, Reunanen 1982, Kannel 1985, Davey Smith 1990, Stoffers 1996, Meijer 1998), some of which have a more or less selected population. In the Edinburgh Study much effort was directed to create a population being as representative as possible. The subjects were, however, recruited from several general practices, thereby excluding those never having attended to such a general practice (Fowkes 1991). In the Whitehall Study and the Basle Study certain working groups were included, prone not to reflect the structure of the general population (da Silva 1990, Davey Smith 1990). In the Limburg Study a very complicated inclusion system was used, undoubtedly in order to include all relevant patient groups, but as a result possibly increasing the effect of patient selection (Stoffers 1996). Some studies have been conducted entirely on population basis. Unfortunately, in these studies claudication prevalence was only investigated by means of a questionnaire (Reunanen 1982, Kannel 1985). A questionnaire is prone not to include all patients with intermittent claudication, as many patients have atypical claudication symptoms. Up to 87% of claudicants have been reported to have atypical claudication (Ögren 2003). The Rotterdam Study was conducted in the population of a suburb, the population of which may not be representative for the whole country. It used resting pressure measurements to determine the presence of PAD. The population included was ≥ 55 years old.

The prevalence of IC has been reported to range between 1,2-6,6 % (Bainton 1994, Meijer 1998, Davey Smith 1990, Reunanen 1982, Fowkes 1991, Stoffers 1996).

The overall 5-year incidence of intermittent claudication has been reported as 2% in men, while the incidence at the age of 70 is 5 times as high as at the age of 40 (da Silva 1990). This is in accordance with the 10-year incidence of 4% in men in the Speedwell Study age group (Bainton 1994) and the 4-year incidence ranging between 0.4 and 2.5 in different age and gender groups in the Framingham Study (Murabito 1997).

6.3.3.1 Prognosis of intermittent claudication

Intermittent claudication itself can be regarded as an annoying and limiting complaint but not threatening the viability of the leg. In most patients the symptoms remain stable or may even improve (Coran 1966, Bloor 1961). In a study by Dormandy et al conservatively treated claudicants were followed. All in all 5,6% deteriorated significantly and 1,6% required amputation within the first year after diagnosis (Dormandy 1991). Similarly, in a study by Jelnes et al only about 7,5% of the patients developed symptoms of critical leg ischaemia during the first year and 2,2% in the subsequent years (Jelnes 1986). Thus, only a small proportion of claudication patients will deteriorate to an extent resulting in a threat to the leg. Low toe pressures seem to point towards disease progression and worse prognosis (Bowers 1993). Likewise there is evidence of continued smoking, diabetes, hypertriglyceridaemia and coronary heart disease to be associated with disease progression (Smith 1996, Dormandy 1999c).

Claudication is, however, associated with a reduced life expectancy and an annual mortality rate of 4.3% (Dormandy 1991). The mortality rate has been reported to be twice as high as in the normal population (Jelnes 1986), mainly due to other manifestations of the arterial disease (Jelnes 1986, Leng 1996). It is estimated that claudication patients' mortality rates resembles that of a general population being 10 years older (Bloor 1961). In fact, in a historical study by Boyd, Ratcliffe and Bloor, the reduced life expectancy has been found to represent a more significant issue for the prognosis of claudication patients than the progression of the lower extremity symptoms (Bloor 1961).

6.3.4 Critical leg ischaemia

The most severe form of occlusive arterial disease in the lower limbs is classified as critical leg ischaemia. 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. Most often a symptomatic classification is applied to determine the existence of CLI (Table 2) but, as not all patients with rest pain, ulcers or gangrenes do have their leg immediately threatened, more precise criteria for critical leg ischaemia have been developed. They are based on both symptoms and objective pressure measurements (Second European Consensus Document 1992, Ad Hoc Committee 1986, Rutherford 1997) (*Table 4*).

Table 4: Criteria for chronic critical leg ischaemia

	ankle pressures		toe pressures		symptoms
European criteria (Eur cons doc)	≤ 50 mmHg	or	≤ 30 mmHg	with	rest pain, ulcer or gangrene
Criteria of the Ad Hoc Committee (Rutherford 1997)	< 40 mmHg	or	< 30 mmHg	with	rest pain
	< 60 mmHg	or	< 40 mmHg	with	minor or major tissue loss

These definitions produce a more objective tool for research purposes but they still exclude patient groups in which the term critical leg ischaemia would be justified and include patients whose leg is not immediately endangered. Furthermore, these definitions do not include ABI-values as it is felt that the absolute pressure and actual blood supply at ankle level is more relevant for the outcome of the foot than the relative pressure (Rutherford 1997, Raines 1976). Single pressures are, however, more vulnerable than pressure indices with greater variation according to the systemic pressures (Baker 1981, Lepäntalo 1983, TASC 2000). The problem in defining critical leg ischaemia is reflected in the differing results achieved by treatment of CLI. In many series differences may be mainly caused by patient selection.

On population basis there is little information on the actual prevalence or incidence of CLI. CLI itself is difficult to assess on population basis, therefore all calculations are based on different assumptions and projections. As critical leg ischaemia is a more severe form of occlusive arterial disease than claudication and results from more extended vascular lesions, it is intellectually appealing to assume that the disease progresses from asymptomatic to claudication and from claudication to rest pain and eventual tissue loss. Some calculations are indeed based on this stepwise progression of the disease and are calculated from prevalence numbers obtained for symptomatic claudication (TASC 2000). The incidence of CLI is estimated to be approximately 300/million/year using a claudication prevalence of 3% and assuming that 5% of these will deteriorate and develop CLI (TASC 2000). These estimates exclude those asymptomatic patients, who never experience claudication but develop CLI without preceding symptoms. The fact that an imbalance between the available blood flow and the demand created by exercise is needed to develop symptoms of claudication, explains in part why critical ischaemia is sometimes the first manifestation of occlusive arterial disease. Especially sedentary patients often do not move enough to develop claudication pain (Dormandy 1999c). When considering the possible effect of neuropathy and the large proportion of diabetics among CLI patients, even rest pain may be absent and the initial symptom may be an ulcer or a gangrene (Jelnes 1986). Furthermore, there is evidence that the severity of symptoms at the moment of occlusion of a proximal segment (for instance superficial femoral artery) is determined by the distribution of pre-existing arterial lesions at calf level (Aston 1992). Even asymptomatic patients may have lesions at calf level and their extension determines the nature of the symptoms occurring later as the disease progresses (Aston 1992). Some develop claudication and others rest pain (Aston 1992). Therefore the assumption of the linear progression of the disease appears to be false, and the prevalence numbers calculated from the prevalence of claudication are unavoidably too low. In a multicenter study by the I.C.A.I.-group in Italy

14 % of critically ischaemic patients presented without preceding symptoms of claudication (I.C.A.I.-group 1997).

In a British survey based on the reports provided by a sample of vascular surgeons, the incidence of CLI was estimated to be 400 /million /year (The Vascular Surgical Society of Great Britain and Ireland 1995).

In Italy Maria Catalano calculated the incidence using three different methods: 1) a prospective 7-year follow-up of 200 claudication patients and 190 controls, 2) a prospective three month sample on CLI-hospitalisations in a number of hospitals and 3) a 6-month – 2-year encoding of major amputations in two regions (Catalano 1993). In the group of claudication patients followed over a period of 7 years, 8 developed CLI, which equals 9 cases of CLI in a population of 1000 claudication patients per year. She used the assumption that 5% of the population above 45 years of age has peripheral arterial disease, as a basis of CLI-incidence calculations. Based on the hereby-obtained CLI-incidence the major amputation incidence was calculated on the assumption that 25% of all CLI-patients will eventually undergo amputation. In the hospital sample 130 hospitalisations for CLI were recorded, which was extrapolated to represent 2 320 CLI hospitalisations in the whole region. The incidence was calculated based on this observation. In assessing the major amputations in two different regions, only the most extensive amputation was included in order to avoid multiple inclusion of the same patient. During the study period of 6 months, 71 major amputations were recorded in Lombardy and 235 were recorded during the two-year-period in Emilia Romagna. According to the calculations the CLI incidence in a population of >45 years of age ranged from 450-652/million/year and the amputation incidence ranged from 112-172/million/year (*Table 5*). Although being based on several assumptions with inherent weaknesses, these incidence estimations might be as close to reality as anyone has got up to now (Catalano 1993).

Table 5: Incidence of critical leg ischaemia according to Italian data (Catalano 1993)

	Incidence (number/million/year)		
Population above 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

In the TASC-document it is proposed to calculate the CLI incidence using major amputation numbers, assuming that 90% of all major amputations are performed for ischaemia and that 25% of all critically ischaemic patients will ever require a major amputation (TASC 2000).

Critical leg ischaemia is by and large caused by multisegmental disease with the vascular tree widely and severely damaged. Reconstructive procedures in critically ischaemic legs can never restore the blood flow to peripheral tissues completely. Intimal hyperplasia, late disease progression and technical problems, thrombophilia as well as compromised runoff may cause the vascular or endovascular revascularisation to occlude (Bergqvist 1996). This necessitates follow-up (Lundell 1995, Sumner 1995), graft corrections as well as new reconstructive procedures to avoid amputation. Nevertheless

many patients end up being amputated when the possibilities for reconstructive procedures are exhausted and the reconstructive procedures have merely been enough to delay the amputation. It has been recommended that if there is a 25% chance to provide the patient a functional leg for a year by means of reconstructive procedures it is worth trying (European Consensus Document 1992).

As critical ischaemia occurs mainly in the last decades of life, many patients are unable to adapt themselves to the use of a prosthesis, due to comorbidities. Even factors such as depression, limited rehabilitation resources, joint contractures as well as phantom pain may render prosthetic fitting more difficult. Therefore a major amputation may lead to immobilisation and institutional care (Inderbitzi 2003). It has been shown that a very active reconstruction policy is able to diminish amputation rates (Luther 1994), even in octogenarians, whose treatment results are similar to those of younger age groups (Eskelinen 2003, Luther 1997b, O'Brien 1993, Nehler 1993).

The mortality of critically ischaemic patients is high. The one-year mortality rates range between 20-25%, 40-70% in five years (Dormandy 1999) and 76-88% in 10 years (Lassila 1986, De Weese 1977). (*see Table 10a-c in Chapter 6.6.2*). Early amputation rates range between 10-40% (Dormandy 1999) with ulcers and low pressure values indicating an adverse outcome (Wolfe 1997). If the amputation can be delayed by revascularisation, it may be possible to retain a functional leg for the short remaining lifetime of the patient. A functional leg may ensure that the patient is able to lead an independent life at home, instead of being confined to a wheelchair and being transferred to institutional care.

6.3.4.1 Subcritical leg ischaemia

There is a patient group, with or without claudication, but with no symptoms of CLI, that has objective pressure measurements indicating decreased perfusion to an extent that critical leg ischaemia may occur (Wolfe 1997). This group is sometimes classified as having subcritical leg ischaemia. These patients are at the brink of developing CLI (Bowers 1993) and as soon as some small trauma occurs, the wound will most probably develop into a non-healing ulcer. In these cases the blood supply is still able to maintain the viability of the intact skin, but as soon as some defect is present, the capacity of the vasculature is not large enough to enable the healing process. It is estimated that, in comparison to intact skin, an ulcer needs a much larger nutritive flow to heal (Laing 1998, TASC 2000). In subcritical patients attention should be directed towards skin care and measures should be taken to prevent small injuries of breaking the skin barrier (Bowers 1993). Maintaining an intact skin is crucial, as each ulcer constitutes a major threat to the viability of the leg.

Another patient group that might be classified as subcritically ischaemic comprises patients with ischaemic wounds but pressure values above those stated in the Second European Consensus Document or the Rutherford criteria. Clinically speaking, these patients may be critically ischaemic (Belch 1995, Thompson 1993) but would be classified in research projects, complying with the consensus documents, as only subcritically ischaemic. Therefore, revision of the definitions has been demanded (Thompson 1993) and as a result the most recent consensus document, the TASC-document, does not include mandatory pressure values in the definition of CLI (TASC 2000). Thus the old Fontaine classification is still practical for clinical purposes.

6.3.4.2 Acute-on-chronic ischaemia

Acute ischaemia is caused by abrupt occlusion of the arterial tree. It produces a sudden deterioration of the oxygen supply and nutritive flow of the leg. When the occluded segment is large and if no collaterals exist, the viability of the leg is threatened and immediate treatment is needed. Acute-on-chronic ischaemia is caused by thrombus formation in a diseased artery, and is to be distinguished from acute ischaemia, caused by embolic occlusion of an often healthy vessel (Jivegård 1986). The distinction is sometimes difficult (Kauhanen 1995, Takolander 1992). In a study by Kauhanen 48% of acute ischaemia was categorised as embolic and 36% as thrombotic, while in 16% the distinction between the two could not be made. Similar proportions were seen in a study in Great Britain where 41% of acutely ischaemic legs were considered to be caused by a thrombosis, while 38% were deemed to be caused by emboli, 15% by occlusion of a bypass graft or angioplasty, 3% popliteal aneurysm, trauma in 2% and iatrogenic reasons in 2% (Campbell 1998). A significant proportion (43%) of patients with acute-on-chronic ischaemia are reported not to have any prior symptoms of PAD in a surgical series (Nypaver 1998), which does not facilitate diagnosis.

Over the years, the proportion of embolic events in acute ischaemia has been declining while the proportion of acute-on-chronic ischaemia has been increasing (Swedvasc Steering Committee 1998, Luther 1995). Improved diagnostic possibilities may in part account for this change, but some of it may also have been caused by a genuine change in vascular morbidity. For ischaemia, occurring acutely in a prediseased artery, the same risk factors apply as to general PAD (Dormandy 1999b). Additional risk factors, such as thrombophilia, low flow states and malignancies constitute a significant risk for developing acute-on-chronic ischaemia (Dormandy 1999b). Mortality rates range from 9.9% and 22 %, while early amputation rates between 7.1 and 16% are reported (Nypaver 1998, Campbell 1998). In a study by Luther et al early mortality was even higher i.e. 27%. One-year mortality was as high as 49%. Early amputation rates were 14% in patents with emboli and 24% in patents with thrombosis (Luther 1995). Patients with an embolic event are reported to be at a higher risk of early death, due to the underlying cause of embolism, while patients with acute-on-chronic ischaemia are more susceptible to amputation (Kuukasjärvi 1994). In fact acutely ischaemic events cause a considerable proportion of all major amputations. Eskelinen et al reported 16.5 % to be caused by acute ischaemia (Eskelinen, in press).

6.4 Diagnosis of occlusive arterial disease and identification of limbs at risk

6.4.1 Diagnosis of PAD and CLI

Atherothrombotic disease leads to arteriosclerosis of the lower limbs. At first, the disease is asymptomatic, but after its progression to such an extent that the arterial blood flow is significantly compromised, it causes symptoms. The symptoms range from typical calf pain during exercise to rest pain, pedal tissue loss and gangrene. Additionally the symptoms may as well present themselves as numbness of the feet and calf, pain in the thigh or buttock, heaviness and tiring during exercise, coldness or even burning sensation.

In the assessment of vascular surgical patients patient history is of significant importance. In many patients the nature of the disease can be evaluated and a diagnosis made, according to typical symptoms together with typical findings. To confirm the diagnosis, and to distinguish the complaints from other

conditions producing similar symptoms, objective assessment methods are mandatory (Lepäntalo 1997). Ankle-brachial-indices have been shown as more closely associated to leg function than the symptom of intermittent claudication (McDermott 2002). When assessing the possibility of PAD, different health care levels have different access to assessment methods (*Table 6*)

Table 6:	Diagnostic tools available
General practician (primary health care)	clinical examination (pulse palpation), ABI-measurement using CW-Doppler, (Ratschow-test)
General surgical outpatient clinic	clinical examination (pulse palpation), ABI-measurement, (Ratschow-test, duplex Doppler)
Vascular surgical clinic	clinical examination (pulse palpation), ABI-measurement, toe pressure measurement, pulse volume recording, (treadmill test, reactive hyperaemia test), duplex Doppler, angiography, MRI, ($TcPO_2$ or other microcirculatory assessment methods)

A part of the clinical evaluation of occlusive arterial disease is pulse palpation at different levels. Pulse palpation has widely been used in everyday practice and many prevalence studies on arteriosclerosis rely on pulse palpation as an assessment method. Although having the advantage of being easy to perform without special equipment, serious concern regarding the reliability of pulse palpation has been expressed. An absent pulse is not always a sign of atherosclerosis, in fact up to 12% of arteria dorsalis pedis pulses have been reported to be congenitally absent (Barnhorst 1968). Only 18 % of pathologic angiographic findings could be identified by absent pulses in the Basle study (da Silva 1980). Inter-observer-agreement of pulse palpation has been reported as unacceptably low (Magee1992, Meade 1968, Ludbrook 1962). When evaluating the presence of the disease a false negative finding is less acceptable than a false positive finding (Dormandy 1992). The consequences of mistaking the pulses, and thereby the vascular status, for normal in the presence of truly compromised vascular flow are much worse than conducting additional vascular assessments after erroneously detecting missing foot pulses (Dormandy 1992).

6.4.2 Identification of patients at risk to lose their leg

In order to slow down disease progression by secondary preventive measures, it would be beneficial to identify patients with PAD as early as possible. This may be difficult, as patients do not seek help unless the symptoms of arterial occlusive disease are severe enough. If the symptoms have a slow onset, the patient does not necessarily realise that it might be worthwhile to seek medical help early on. A sudden onset on the other hand, usually causes the patient to see a doctor, especially if the pain is severe. Patients having neuropathy, due to diabetes or other causes, may not experience pain caused by

ischaemia during exercise (Jelnes 1986). They may even be totally unaware of the presence of an ulcer - often developing after a small injury (Pecoraro 1990). Due to the large range of symptoms there may be considerable delay in seeking medical help and appropriate measures cannot always be taken in time.

If symptoms indicating critical leg ischaemia are present, measures to restore sufficient blood flow to the ischaemic tissues should be undertaken in due course. According to a consensus statement the patient should be sent to a vascular surgical unit within 24 hours for proper assessment and to receive possible reconstructive measures (Audit Committee of the Vascular Surgical Society of Great Britain and Ireland 1996). In everyday life patients are, however, seldom admitted within 24 hours, so treatment delay can be considerable (Bailey 2003). Thus the identification of patients with limbs at risk is of utmost importance at any level of the health care system.

In primary health care, where a large number of people present with a whole spectrum of symptoms, it can be difficult to distinguish those patients in need for further assessment or even those who need urgent evaluation and treatment. Pain during exercise may be interpreted as caused by orthopaedic disorders such as arthrosis and spinal stenosis. Pain at rest may similarly be caused by arthrosis, traumata, neuropathy, infections etc. and the ischaemic aetiology is often difficult to distinguish properly. Even ulcers can be treated for months with antibiotics and local dressings before the vascular status is evaluated, especially when an ulcer seems to have an innocent cause such as an injury. Early diagnosis and treatment are mandatory in diabetic foot lesions as they carry a high risk for major amputation (Lepäntalo 2000). In contrast, prompt multidisciplinary treatment of the underlying cause of the diabetic foot lesions has produced encouraging results in terms of limb salvage (Lepäntalo 2000).

6.4.3 Vascular laboratory and angioradiology

6.4.3.1 History

To study physiologic phenomena, plethysmographic measurement methods have been described already in the 1600's (Johnson 1932). To study vascular responses and physiology different plethysmographic and oscillometric devices have been developed (Johnson 1932). The first arterial pressure measurement was performed invasively on the carotid artery of a horse in 1733 by Stephen Hales (Pernow2002). Non-invasive arterial pressure measurement, using external pressure together with a smygmograph, was first introduced by Karl Vierodt in 1855 and developed further by Marey and others (da Silva 1990). Pressure measurements gained wider acceptance when Sciapini Riva-Rocci demonstrated a cuff that was placed around the arm in 1866 (Pernow 2002). The cuff was inflated to 200 mmHg and slowly deflated until the pulsation of the radial artery reappeared. Nikolai Korotkoff modified the measurement using a stethoscope and could by that means detect both the systolic and diastolic pressure (Pernow 2002). This method could, however, not be reliably applied on the assessment of occlusive disease in the distal arteries of the leg. Gärtner introduced in 1899 a method where the detection of distal systolic pressure based on filling of the capillaries, but this method was not very reliable (Pernow 2002). One of the first pressure measurements on lower limbs to study arteriosclerosis has been performed by André Thomas in 1918 using a smygmograph (da Silva 1980). Ejrup seems to have been the first to introduce pressure measurements after exercise using oscillographic methods (Ejrup 1948).

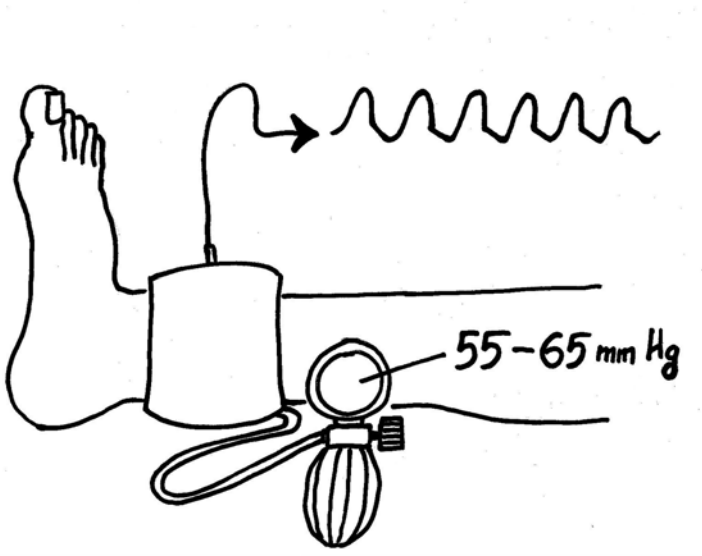
6.4.3.2 Methods

6.4.3.2.1 Pneumoplethysmographic measurement methods

Oscillometry is performed using a pair of cuffs attached to a pressure sensor and a plotter. The pressure in the cuffs is inflated above the systolic pressure and lowered slowly while the oscillations are recorded. For evaluation the maximal amplitude of the oscillations is measured and compared (Windus 1952, Windus 1953). Before the widespread availability of routine angiography and Duplex-Doppler scanning, segmental pressure measurements and oscillometry were used for determination of the level of arterial disease. This method has been replaced widely by Duplex-Doppler scans.

Pulse volume recording (PVR) is the recording of pulse waves using pneumoplethysmography (Winsor 1957, Raines 1976, Darling 1972). PVR measurements are performed by inflating the cuff to 55-65 mmHg and by registering the pulse waves (*Figure 4*). The amplitude as well as different aspects of the curve can be assessed. PVR was used to detect occlusive arterial disease. As the method has been seen to be of limited reproducibility and susceptible to disturbances, its role today is mostly that of an indicator for the reliability of pressure measurements (Lepäntalo 1997).

Figure 4: A schematic illustration of pulse volume recording



A recent development of traditional pulse volume recording is the transfer function index measurement, which utilises the philosophy of PVR recordings and compares the obtained curves by means of Fourier analysis. PVR curves are recorded simultaneously at up to 10 different sites for a certain period of time. The obtained curves are averaged, thus minimising the effect of beat-to-beat variability. The averaged curve is compared with the curve obtained at the previous or brachial segment using Fourier transformation and a transfer function index is calculated. This method offers promising features for vein graft surveillance, as it has been shown to be reliable in detecting compromised graft flow (Ihlberg 2001), but further investigation is needed before its introduction into routine clinical use.

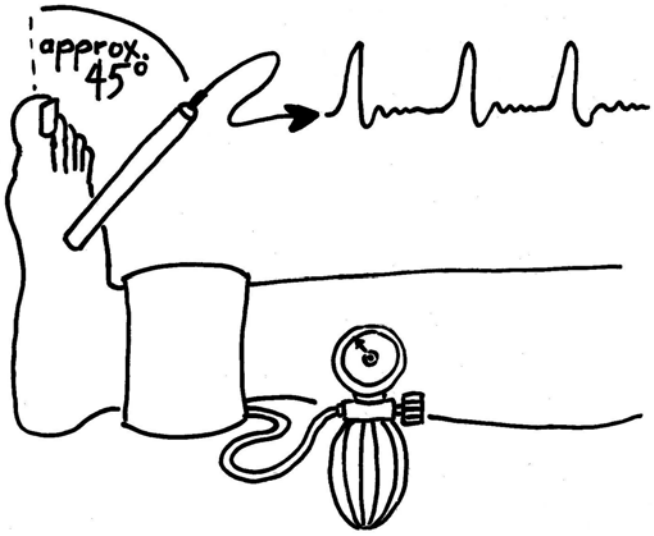
6.4.3.2.2 Pressure measurements

Distal pressure measurements have established their role as the basic haemodynamic assessment method for vascular patients. Measuring pressures is a quantitative assessment method and allows some conclusions as to the severity of the disease (Carter 1968). They have been performed using different plethysmographic methods (Carter 1968, Strandness 1964), as well as Doppler signals (Satomura 1959, Strandness 1966, Yao 1969) to detect the reappearance of blood flow distal to an occluding cuff. The pressure of the cuff is raised well above the systolic pressure, then released slowly to detect the pressure level at which the blood flow signal reappears. To eliminate the confounding effect caused by the variation of the systemic pressure, either an ankle-brachial index (ABI) (Yao 1969) or an ankle-brachial gradient is calculated, of which the ABI has been found to be more reproducible (Baker 1981).

Normally the systolic pressure of the leg exceeds the pressure of the aorta and brachial vessels due to compliance of the vessel wall (Remington 1956); therefore the ABI of the normal leg should exceed 1.0. When measured by experienced measurers, the measurement variability has shown to be reasonable with 0.15 representing a significant difference between two measurements (Baker 1981, Fowkes 1988). In case of very low (<100 mmHg) as well as very high (>200mmHg) systemic systolic pressures, the ankle pressures have, however, to be handled with caution as they have been observed to be about 25% lower than the aortic pressure without evidence of PAD (Belcaro 1989).

The most widely applied method for measuring the ankle pressures is using a CW-Doppler as the means of detecting blood flow (Jeelani 2000) (*Figure 5*). It has the advantage of being relatively easy to perform and provides the possibility of measuring pressures in each vessel separately. Furthermore the devices needed are inexpensive and are usually included in the basic equipment of each hospital and health care centre. The simplicity of the measurement technique is, however, deceptive and it has been shown that up to 30 % of measurements performed by inexperienced measurers lie outside the accepted range of variability of 0.15 in ABI measurements (Baker 1981, Ray 1994). In a Dutch study, where the measurers were general practitioners (and their assistants), the measurement variation lay between 15-20%, which is clearly higher than the generally accepted range of variability (Stoffers 1991). Therefore the measurements of inexperienced measurers should not be used as quantitative, but only as qualitative measurements. In the hands of an experienced measurer the CW-Doppler provides us with a useful, reliable and reproducible assessment tool for measurement of peripheral systolic blood pressures (Baker 1981, Lepäntalo 1983). Reproducibility observations of ABI measurements have largely been made either among healthy individuals (Fowkes 1988), unselected patients attending a vascular laboratory (Ray 1994, Stoffers 1991) or claudicants (Baker 1981, Kaiser 1999, Fowkes 1988), not in patients with CLI. All international consensus criteria, including non-invasive assessment for critical leg ischaemia definition, use mainly absolute ankle pressures. ABI-measurements are, however, important for the clinician both at the time of diagnosis and during follow-up (Ramsey 1983).

Figure 5: A schematic illustration of ankle pressure measurements using a CW-Doppler probe

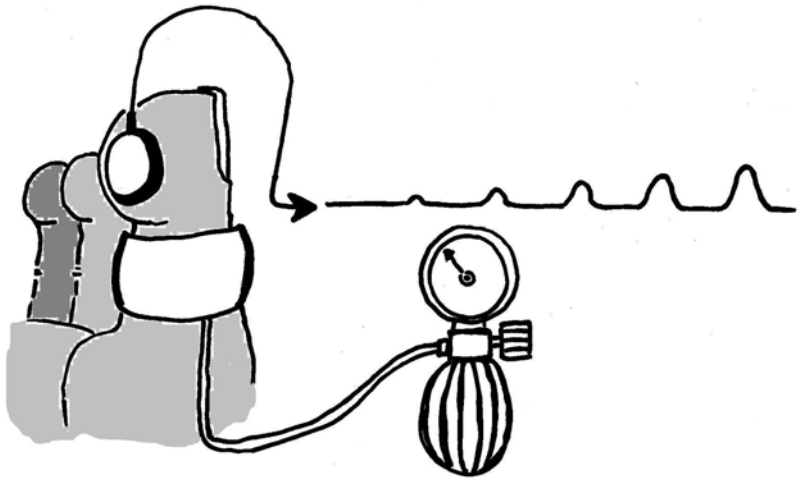


Using the Doppler technique it is only possible to measure the flow in larger vessels – toe pressure measurements need either strain gauge plethysmography or photoplethysmography as means of detection of the reappearing blood flow.

Toe pressure measurements with strain gauge plethysmography are performed using an elastic silicone tube filled with mercury as an electric resistor. This silicone/silastic tube is placed tightly around the toe distal to the occluding toe cuff. When the pressure in the cuff is lowered and blood flow reappears in the toe the volume and circumference of the toe grows, the tube stretches and the resistance of the mercury inside the tube changes and can be recorded. (Nielsen 1972, Lezack 1970, Gundersen 1971) The method requires a stock of several strain gauges of different sizes, as a tight fit is necessary to perform the measurement. It also requires some specialised equipment and expertise to achieve reliable results. Using this method even non-pulsatile flow can be detected (Nielsen 1972, Lassen 1976) and thus very low pressures can be measured. Disadvantages of the method include the sole applicability on circular body parts where close contact to the underlying tissue is maintained along the whole circumference (Linde2002). Another disadvantage is the toxic quality of mercury, which poses a threat to the health of employees and the environment (Linde 2002). Finally the strain gauge is temperature-sensitive, with its resistance varying according to the surrounding temperature (Linde 2002).

The strain gauge technique has been widely replaced by the photoplethysmographic technique (*Figure 6*), which has the advantage of being easier to interpret and having one probe fitting each toe, forefoot or finger. The photoplethysmography probe sends infrared light into the tissue. It is reflected with varying intensity depending on the presence of erythrocytes. With increasing erythrocyte content in the tissue, the reflected light diminishes. Using the photoplethysmographic technique pulsatile blood flow is needed, which makes the technique less sensitive than strain gauge plethysmography in detecting flow signals at low pressure levels. At pressures below 30 mmHg Doppler waves become flat, lose their pulsatility and are difficult to detect using the photoplethysmographic technique.

Figure 6: A schematic illustration of toe pressure measurements using photoplethysmographic technique



Pressure measurements can be performed in segments to determine the level of arterial lesions. Lower limb pressure measurements above the ankle level have become scarce as the level and the morphology of the changes is usually determined by Duplex-Doppler and angiography if the indication for a reconstructive procedure is present.

In the assessment of claudication, the walking distance has been used as the measure of severity of lesions. The anamnestic walking distance is, however, very imprecise, as the estimate of the same distance has been seen to be subject to huge variation (Watson 1998, Peräkylä 1998a). Therefore, more standardised estimates of disease severity in claudicants are needed. Different exercise tests have been developed: treadmill tests, heel raisings and plantar flexion of the foot (Strandness 1964, Myhre 1975b, Winsor 1959, Amirhamzeh 1997)

6.4.3.2.2.1 Stress tests

The most frequently used method is the treadmill exercise test with or without pressure measurements. Using the treadmill, the actual walking distance can be measured, although the reproducibility of the walking distance is very poor and a marked learning curve improving the walking distance in repeated measurements has been observed (Peräkylä 1998b, Laing 1986, Guyatt 1984). The decrease in ankle pressures following a short exercise with inclination has been seen as being more reproducible than the walking distance itself (Laing 1980). A short exercise provides equally reliable results as longer treadmill tests (Laing 1983, Laing 1986). When comparing different methods of evaluating the pressure drop after exercise, expressing the ankle pressure change as a percentage of the absolute resting pressure, has been shown to have the smallest variability (Amirhamzeh 1997). As symptomatic occlusive arterial disease is known to reflect the situation in the whole vasculature, a short treadmill exercise has the additional advantage of not causing additional cardiac complications (Laing 1980). The treadmill test may provide a rough estimate of the cardiac condition and may be useful in predicting peroperative cardiac complications in PAD patients (von Knorring 1986, Mc Cabe 1981, Cutler 1979).

In the case of a treadmill test not being feasible or available, a reactive hyperaemia test can be performed instead. (Myhre 1975b, Hummel 1978) The reactive hyperaemia test is performed using a broad cuff at thigh level. This cuff is inflated to 300 mmHg and the pressure is kept for 3-5 minutes in order to cause an acute ischaemia in the limb. After pressure release the haemodynamic reaction in the lower limb is measured using either pressure measurements at ankle level, maximal velocity time or other means of measurement. During ischaemia vasoactive mediators are produced and the arteries are dilated (Fronek 1973). Therefore, the vascular resistance in the periphery is low in the reactive hyperaemia test, with an increased demand of arterial flow. The flow past an occluded arterial segment or a significantly stenosed artery with a diminished flow reserve will not be able to meet this increased demand and a pressure drop, or an increased maximal velocity time, will be measurable. The reactive hyperaemia test has been shown to be a reliable and reproducible substitute for the treadmill test (Peräkylä 1999, Hummel 1978), but its applicability is restricted by the fact that it is often very painful (Carter 1968, Leng 1996).

6.4.3.2.3 Problems related to measurement techniques

There are several limitations to the use and interpretation of pressure measurements (*Table 7*).

Table 7: Limitations of pressure measurement methods

Method	Principle	Problems
Ankle pressure:	occluding cuff, distal detection	mediasclerosis, cuff width, systemic pressure, patient movement
- CW-Doppler	hand held probe, readily accessible flow signal quality evaluable	operator dependent, especially with low signals
- PPG	probe attached to toe/forefoot, less operator dependent	needs pulsatile flow
Toe pressure:	occluding cuff at toe level distal detection seldom affected by mediasclerosis	low reproducibility, great physiogical variation susceptible to vasospasm influenced by temperature changes
-strain gauge	does not need pulsatile flow, low pressures measurable	operator dependent, several strain gauges needed, toxic
-PPG	less operator dependent one probe fits all	low pressures not reliably measurable

CW= continuous wave
PVR= Pulse volume recording
PPG= Photoplethysmography

Thigh, calf or ankle pressures can be falsely high if a too narrow cuff is used. The width of the cuff should be at least 120% of the diameter of the measuring site.

Similarly the pressure values will be falsely elevated if the wall of the vessel is stiffened because of mediasclerosis. Such mediasclerotic vessels need a higher pressure to be compressed or can be even non-compressible. Mediasclerosis is mainly caused by diabetes, uraemia or systemic corticosteroid treatment (Goss 1989, Leskinen 2002, Mc Millan 1997). Most of all it affects the larger vessels of the lower limbs, but brachial vessels are sometimes affected as well (Edmonds 1982). It affects the elasticity of the artery, destroying the autoregulation of the vessels. Although non-invasive pressure values seem to be normal or good, blood flow can be severely impaired. If the ABI is clearly elevated (>1.3) or the vessels are incompressible, it is easy to recognise a falsely elevated ankle pressure value (Carter 1985). It is even recommended to suspect pseudohypertensive elevation of ankle pressures when ABI exceeds 1.15 (Takolander 1995). Routine performance of pulse volume registrations is recommended (Carter 1968, Goss 1989) as well as routine toe pressure measurements. When a discrepancy between pressure values and the amplitude and shape of the PVR curve is present, the pressure values are interpreted to be pseudohypertensive and unreliable. Mediasclerosis does, however, produce also partially incompressible arteries and does therefore elevate ankle pressures at all pressure levels (Young 1993, Goss 1989, Emanuele 1981), which is difficult to detect if the values are still compromised in conjunction with flattening of the PVR curves. As the vessels of the toes are in general not affected by mediasclerosis - although exceptions may occur (Young 1993) - toe pressures should be used instead in these cases.

Toe pressures have, however, some pitfalls of their own. Blood flow in the small vessels of the toes underlies great physiological variation (Burton 1939). These vessels are more prone to vasospasm than larger vessels. Consequently, significantly lower pressure values are measured with toe temperature at 10 degrees Celsius, as opposed to measurements performed at room temperature (Sawka 1992). Significant vasospasm has been shown to exist even at room temperature in routine measurement conditions (Sawka 1992). In order to minimise the effect of vasospasm the patient is to rest in a warm room or under a warming blanket prior to toe pressure measurements. Additionally the feet may need to be heated before the measurement, especially in winter.

Another proposed measurement technique for the assessment of patients with assumed low pressures but pseudohypertensive ankle pressures is the so-called pole test (Smith 1994, Sambraus 1996, Beyenal-Ögmen 1999). The pole test is performed with the patient in supine position using the CW Doppler to listen to the signal of a dorsal artery. Instead of using a cuff, the leg is elevated slowly and the level at which the signal disappears is read using a vertical centimetre scale on a pole (cm H_2O). After that the pressure values (mmHg) can be calculated. Pressure measurements have been observed to have a good correlation with pressure measurements using a cuff (Hiller 1998).

The patient's inability to hold still or severe pain at the site of the cuff may be a problem in the technical performance of the measurements, sometimes causing all attempts to obtain a measurement to fail. Similarly, atrial fibrillation or other cardiac arrhythmias may hamper the gathering of reliable measurements.

6.4.3.2.4 Microcirculatory measurement techniques

Additional microcirculatory assessment techniques, such as transcutaenous oxygen tension ($TcPO_2$) measurements, laser Doppler fluxmetry and nailfold microscopy (Fagrell 1999) can be used to determine tissue viability and predict outcome (Ubbink 1999, Wahlberg 1993), especially in critically ischaemic patients if pressure measurements cannot be performed (Ubbink 1993). $TcPO_2$ measurements have low reproducibility in critically ischaemic legs, even if being well applicable in healthy legs (Lukkari-Rautiainen 1989). Overall the reproducibility of microcirculation assessment methods does not seem to be as good as the reproducibility of measurement methods for macrocirculation (Lukkari-Rautiainen 1989, Ubbink 2000) and none of these have achieved large clinical use. This may be explained by the great physiologic autoregulatory function of the microcirculation (Shore 1993). The microcirculation responds more readily to exogenous and endogenous vasoconstricting and vasodilating stimuli. Therefore the conditions in which microcirculation is measured have to be strictly standardised (Larsen 1990, Fagrell 1999, Ubbink 2000) and additional standardised stimulation tests such as reactive hyperaemia or oxygen inhalation should be used (Jacobs 1992, Bongard 1988, Diamantopoulos 1994). The method of microcirculatory measurement seems to be of importance as different methods measure different aspects of the microcirculation: capillary microscopy is limited to the nutitive capillary flow, while both laser Doppler fluxmetry and TcPO2 seem to measure also the thermoregulatory flow (Fagrell 1999). A combination of methods such as laser Doppler fluxmetry and capillary blood cell velocity measurement with an index of these two may produce the most reproducible results (Fagrell 1999). Laser Doppler fluxmetry has, additionally to the resting flux, been seen to oscillate over time in relation to vascular autoregulation (Fagrell 1999). Normally only low frequency oscillations are visible, but in critically ischaemic patients also high frequency oscillations are observed (Anvar 2000). This phenomenon is not affected by oedema or limb position (Anwar 2000) and it may be the more significant feature when measuring microcirculatory flux, using it to determine the degree of ischaemia (Fagrell 1999).

6.4.3.2.5 Other assessment methods

Among other techniques that have been used for vascular assessment are temperature measurements and the dilution of radioactive Xenon (Lassen 1972). Skin temperature is, however, influenced by many factors such as room temperature, humidity, metabolic state, nervous and vasomotor activity and nicotine (Fronek 1985). It is difficult to standardise all influencing factors and measure only the effect of vasclar blood supply on the skin temperature (Fronek1985). Also the correlation between blood flow and skin temperature is non-linear, which further decreases the applicability of temperature measurements in vascular assessment (Fronek 1985). Radioactive nuclide dilution techniques have failed to provide sharp endpoints and as they are time consuming and expensive, they have been abandoned in routine patient evaluation (Moore 1985, Nicolaides 1985)

6.4.3.2.6 Duplex Doppler

For further assessment of the vasculature of the lower limbs, duplex Doppler is available as a technique combining flow velocity measurement using a pulsed Doppler and morphological assessment by means of ultrasound sonography (Woodcock 1980). Unlike the continuous wave Doppler, the pulsed Doppler utilises a time frame for determination of the target depth (Walker 2002). The transducer determines the

time needed for the Doppler waves to reach target depth and to be reflected from there to the detecting device. Only waves fitting into the time frame will be analysed while all other Doppler-information will be excluded (Walker 2002). The method is thereby suitable for selected velocity measurements. With increasing depth the width of the signal broadens and the resolution deteriorates. Transducers with short wavelengths have an excellent axial and lateral resolution but limited ability to measure velocities while longer wavelengths have a worse resolution, but are able to measure greater velocities (Walker 2002). Concerning the angle of Doppler-derived velocity measurements it would be ideal if it were possible to place the transducer/receiver in line with the blood flow and have the blood cells moving directly towards the probe (Johnston 1977, Walker 2002). As this is not possible a mathematical correction is used, provided that the angle of insonation is known (Walker 2002). Angle compensation will produce reliable results only to a certain degree and measurement error will increase with decreasing insonation angle. Mostly, in order to standardise the technique, an angle of 60-degrees is used, as it provides acceptable measurement results and is usually achievable in everyday use.

The duplex-Doppler, and the so-called triplex-Doppler with a colour coded flow signal, provides a tool for noninvasive evaluation of the arterial flow. Especially in the assessment of and follow-up of vein grafts, as well as in areas of complicated anatomy and arterial bifurcations, the duplex-Doppler has shown its advantages (Sumner 1995). The duplex-Doppler is an operator-dependent non-invasive method with acceptable reproducibility in the hands of experienced technicians (Ihlberg 2000, Müller 2001).

6.4.3.2.7 Angiography

Angiography, whether it is performed using a conventional technique, using magnetic resonance imaging or processing computed tomography information, does still have an important role in the assessment of the preoperative patient. A good quality angiogram, with the vessels visualised down to the pedal arch, gives an excellent overall picture of the morphological changes in the vascular tree. Selective antegrade digital subtraction angiography (DSA) is the "gold standard" in visualising the arterial tree, especially prior to invasive therapy. However, the role of duplex-Doppler is increasing as a preoperative tool as well (Koelemay 2001, Luján 2002). Angiography is usually not a method for the initial assessment of the vascular patient, as it is expensive, invasive (with potential complications) and does not provide information on the actual haemodynamic state of the limb. Thus vascular laboratory and radiological data supplement each other.

6.4.3.3 Identification of patients with critical leg ischaemia

The identification of critical leg ischaemia is mostly based on symptoms such as rest pain, leg ulcers and tissue necrosis (gangrene). Again many other disorders may produce similar symptoms and the ischaemic complaints have to be distinguished from these (TASC 2000). Rest pain may be caused by injuries, arthrosis, arthritis, neuropathy as well as infections. Ulcers are usually caused by injuries, infections or venous hypertension, irrespective of the presence of an impairment of the arterial blood flow. Indeed, most ulcers are of a non-ischaemic origin and it may be difficult to recognise ischaemic ulceration at an early stage, especially as many confounding factors may be present and other causes for ulcers may coexist. Most gangrenes are of ischaemic origin but heat, cold, toxins and infections may cause gangrenes as well.

To distinguish between different etiologic factors contributing to rest pain, ulcers and gangrene non-invasive resting measurements may be used.

Ankle-brachial index measurements in combination with pulse volume recordings and toe pressure measurements are the most frequently used non-invasive measurement methods for CLI diagnosis. For identification of critical leg ischaemia various pressure limits have been proposed (Rutherford 1997, European Consensus Document 1992).

In CLI flow signals are often very low, making pressure measurements prone to measurement error (Ubbink 2000). The multimorbidity often present in critically ischaemic patients may cause difficulties, for instance through cardiac rhythm disorders, shortness of breath in supine position, leg oedema, ulcers, infections etc.

In some obvious cases of CLI and in situations where revascularisation is to be undertaken without delay, the extent of the vascular lesions is primarily investigated using Duplex-Doppler, angiography or MRI-angiography. Preceding haemodynamic assessment with non-invasive measurement methods may not always be available, although baseline data for follow-up purposes may be beneficial and recommendable.

6.5 Outcome assessment

6.5.1 Outcome assessment in claudication patients at risk to develop CLI

As intermittent claudication itself seldom poses a threat to the viability of the leg but is associated with a decreased life expectancy due to involvement of the whole vascular tree (Bloor 1961), outcome assessment in intermittent claudication is bound to concentrate on functional improvement, graft patency, mortality reduction, disease progression and quality of life assessment.

The treatment of intermittent claudication may be directed towards local improvement of the blood flow in the diseased arterial segment through surgical or endovascular procedures, and probably regular exercise, or towards disease and arteriosclerosis stabilisation through smoking cessation and risk factor control. Treatment of the risk factors and possible concomitant coronary disease may improve mortality and overall prognosis (Donnelly 2002).

The outcome assessment can be classified as objective outcome with walking distance and pressure value improvement, symptomatic outcome with pain relief, general quality of life outcome, disease specific quality of life outcome and postrevascularisation outcome with patency of the revascularised segment (TASC 2000).

Objective outcome measuring functional amelioration is often measured using improved walking distance. Although deemed as the most appropriate objective measure of success of treatment of IC (TASC 2000), this technique is very imprecise as the reproducibility of the walking distance is poor (Peräkylä 1998b, Laing 1986). It has been suggested that after therapy an increase of 50-60% in the walking distance would be needed for the change to be regarded as significant. It should exceed the improvement achieved using placebo at least by 30% (Heidrich 1992). Quick found a mean increase of

40% of the maximum walking distance on a flat treadmill in claudicants after smoking cessation (Quick 1982). When using two standard deviations, an 84% improvement or decrease would be needed for a significant change when measuring the maximum walking distance on a flat treadmill, according to Peräkylä. On a flat treadmill the initial walking distance change would have to be as much as 62% to achieve significance. On a graded treadmill the reproducibility is reported as slightly better with two standard deviations of 36% for the maximum walking distance and 58% for the initial walking distance respectively (Peräkylä 1998b).

Ankle pressures are suggested to be more reliable in determining improvement of blood circulation after treatment (Peräkylä 1998b). A significant difference should be calculated for each laboratory separately. In general an ankle brachial index change of 0.15 is widely used (Baker 1981, Ray 1994), but the use of 0.1 has been recommended too (Ad Hoc committee on reporting standards 1986, Rutherford 1997). Of these the latter appears to be based on consensus rather than on referred published data. Haemodynamic success of a procedure will not be guaranteed automatically if the graft, or endovascularly treated segment, is patent but can be assumed if the ankle brachial pressure index is improved significantly.

Symptomatic outcome and general quality of life outcome may be assessed using different questionnaires. The surgeon's impression of the patient's symptoms, as well as walking distance and ankle pressures, have been shown to have a poor correlation with the results in standardised quality of life assessments (Pell 1995, Barletta 1996, Currie 1995, Hicken 2000, Slevin 1988, Pearlman 1988). Quality of life assessments with subjective pain relief and subjective functional improvement are to be used as a measure for therapeutic success (Garratt 1993). They will gain more and more importance due to limited health care resources (Myhre 1989) where the need for evidence based medicine is emphasised (Fisher 1999).

Generic quality of life assessments have been suspected to be less sensitive to treatment results in vascular patients than disease specific scores (Mehta 2003, Cassar 2003). The use of additional disease-specific scores, such as the walking impairment questionnaire, the VascuQoL and the ICQ may be helpful in assessing vascular treatment results (Hiatt 1995, Morgan 2001, Chong 2002).

Postrevascularisation outcome concentrates on graft and PTA-patency and should ideally be assessed using imaging techniques (TASC 2000).

6.5.2 Outcome assessment in critical leg ischaemia

The outcome assessment measures in critical leg ischaemia are generally the same as in intermittent claudication: graft patency, mortality reduction and quality of life assessment. However, as critical leg ischaemia is a condition endangering the viability of the leg and is associated with considerable co-morbidity and ensuing mortality, the main outcome measures are above- and below- knee amputation rates and survival. It is important to make a clear distinction between small amputations, i.e. toe or even metatarsal amputations and major amputations at calf level or higher. If a necrotic toe is amputated and the rest of the foot remains viable as a result of treatment, the treatment is to be deemed successful. Thus minor amputations should be understood to be comparable to wound excisions or debridements (Lepäntalo 2002). The assessment of CLI outcome and amputation rates can therefore be grossly generalised as "counting the heels". Ideally major amputations and mortality should be combined in outcome analyses, as the major concern ought to be how many patients are alive with a leg at a given moment of time.

Additional outcome measures such as pain relief, wound healing, primary and secondary graft patency, minor amputations, leg functioning, wheelchair use, ability to live independently, walking without support and need for institutional care may be used. Furthermore in this era of limited health care resources coupled with growing demand, cost-descriptions and quality of life assessments are being performed and quantifications such as cost-effectiveness, cost-utility and cost-benefit calculated.

Mortality may be the variable with the most complete coverage, as most countries have some kind of registry to register mortality and death causes. Obtaining amputation data may already be more difficult and will usually rely on the accuracy of hospital records.

Other variables will not be automatically recorded into any registries and demand more explicit study regimens and mainly prospective recording of data.

Collecting data to determine treatment costs includes selection of the data and decisions, which costs are to be included. Very different approaches can emerge and different studies may not be comparable. Some studies include only direct costs for operative treatment, other studies include medical treatment cost, rehabilitation cost, loss of working capacity, costs for re-operation, amputations and institutional care (Luther 1997c).

Quality of life has been shown to correlate with the degree of ischaemia (Klevsgård 1999, Luther 2002). Quality of life (QoL) assessments for critical leg ischaemia are an important feature in the assessment of critical leg ischaemia as a condition. The assessment will, however, be most probably difficult to accomplish in an unselected critically ischaemic population. Many critically ischaemic patients are very old and a major proportion of them are already demented, which makes them prone to failing to complete the questionnaire (Currie 1995). Meaningful quality of life assessment will be difficult to obtain in these patients and a quality of life assessment done by a proxy such as a relative or hospital personnel can only be of very limited value (Hicken 2000). Hernández-Osma et al performed a generic quality of life assessment among critically ischaemic patients without previous reconstructive surgery. More than 30% had to be excluded from the analysis because they were unable to complete the questionnaire and another 14% did not comply (Hernández-Osma 2002). Exclusion of such a major sample will most probably produce selected material, which cannot be regarded to represent all critically ischaemic patients. Although this patient material was selected, representing the less severe CLI-patients, a worse baseline QoL than the reference population was recorded for all QoL dimensions. The quality of life was compared between three groups receiving either revascularisation or amputation or conservative treatment. No differences between these three groups existed, which may be explained by the fact that the co-morbidities, present in most critically ischaemic patients, affect the quality of life to a considerable extent. 12 months after initial treatment the quality of life had in fact decreased in all three groups owing probably to the fact that the overall morbidity of these patients continues to deteriorate regardless of the treatment modality used. (Hernández-Osma 2002). In contrast to this, Thorsen et al conducted a Nottingham health profile investigation among critically ischaemic patients scheduled for an arterial reconstructive procedure. He found a significant improvement that maintained 12 months in pain and sleep scores after treatment (Thorsen 2002). Albers et al assessed the quality of life of critically ischaemic patients dividing the patients into three groups: one with successful arterial reconstruction (15), one with arterial reconstruction but secondary major amputation (7) and one with primary below knee amputation (16). These patient groups were followed for 12 months and were assessed using the Spitzer QL-INDEX. The quality of life score was initially worse in the amputated group than in the reconstructed group. This difference, however, subsided within 12 months while the patient group with secondary amputation had the worst quality of life-score throughout the study (Albers 1996).

6.6 Outcome of CLI

6.6.1 Factors influencing the outcome

Critical leg ischaemia is not a single disease with a uniform outcome for all patients, but rather the result of advanced atherosclerosis caused by different risk factors, which influence the prognosis to a major extent. A wide range of symptoms and underlying arterial lesions is included in the definitions of critical leg ischaemia (Rutherford 1997, Second European Consensus Document 1992). This causes the patient group to be heterogeneous. Although the classification of critical leg ischaemia implies a threat for the viability of the involved tissue, the amputation risk is very different in different subgroups of critical leg ischaemia. Not all patients with CLI require amputation (Ubbink 2000). Suggestions to divide critical leg ischaemia into two categories have been put forward: those with rest pain only and those with ischaemic tissue loss (Thompson 1993). On the other hand the definitions tend to exclude patients, who have a similar threat to lose their leg but do not fulfil the CLI-criteria (Belch 1995, Ubbink 2000). Despite these attempts to widen or narrow the CLI-criteria, the amputation risk and outcome will differ substantially within the patient group.

For ethical reasons the natural outcome of the whole population of critical leg ischaemia cannot be assessed today. Historic studies like the study by Bloor, Boyd and Ratcliffe (Bloor 1960) and the study by Juergens et al (Juergens 1960) give us some hint as to the outcome in this patient group. The advances in both medical and surgical treatment make these series not entirely representative of the patient population today. The outcome of CLI patients will be influenced by both local factors and systemic factors. The mean age is higher today, the overall treatment of the underlying cardiovascular disease bears more possibilities and additional influence can be directed towards the treatment of different risk factors. On the other hand surgical and endovascular treatment have undergone an evolution influencing the overall outcome in CLI.

The adoption of an aggressive reconstruction policy has been shown to reduce amputation rates by 25-63% (Lindholt 1994, Luther 1994, Eickhoff 1993, Eskelinen 2003), which is bound to influence the overall outcome of the patients. In most studies the reductions are reported in absolute major amputation rates without taking into consideration the increasing risk due to ageing of the population. In 1988 Pohjolainen estimated an increase of 50% in amputation rates within the next 20-30years (Pohjolainen 1988). Despite that, an overall decrease in amputation incidence of 41% has been observed from 1984 to 2000 (Eskelinen 2004). Compared to the estimates made by Pohjolainen, the overall decrease achieved by vascular reconstructive procedures was 52% (Eskelinen 2004).

Opposing to the adoption of an aggressive reconstruction policy, a failed bypass graft has been suspected of having an adverse effect on amputation levels (Stirnemann 1992), but this suspicion could not be confirmed (Ebskov 1999, Panayiotopoulos 1997, Tsang 1991).

As to the influence of successful bypass surgery: the patency of a bypass graft has been seen to correlate well with the overall clinical outcome of the leg, but exceptions may occur (Watson 1999). Some critically ischaemic legs end up being amputated in spite of a patent graft. This is typically observed in patients with large, deeply infected tissue lesions (Lepäntalo 2002) On the other hand not all graft occlusions necessitate amputation (Watson 1999). Especially in cases in which the bypass flow has enabled the lesion to heal, later graft occlusion may be well tolerated (Mätzke 1997, Zdanovski 1998).

Different risk factor profiles may affect the outcome. Diabetes may be the most obvious risk factor with a reported 10-fold mortality rate and a 5-fold amputation rate compared to other PAD-patients (Meillère 1999). In a recent British study the proportion of revascularisations was similar in diabetics and non-diabetics, but the major amputation rate at follow-up was 26% in diabetics and 8% in non-diabetics (Bailey 2003). Apart from diabetes, other risk factors may contribute to differing results as well.

The outcome as such may be influenced by referral practices, as diagnostic difficulties and referral patterns can delay the treatment. Patients with CLI often have symptoms for many weeks before being seen by a specialist: the duration of symptoms ranged between 2 weeks to 1,5 years in a British study (Bailey 2003), which is in discordance with the recommendation on the referral of CLI patients (Audit Committee of the Vascular Surgical Society of Great Britain and Ireland 1996).

Similarly, socio-economic factors, can influence the outcome in PAD, as has been seen in cardiovascular diseases (Salomaa 2001, Engström 2000, Morrison 1997). Socio-economic factors may be speculated to influence the outcome through differences in the risk profile as such, but also through the patients' readiness to seek medical help, their compliance, disease treatment and prevention as well as hospital funding.

Finally the reporting of results can influence the outcome figures, making results from different series not comparable. Especially the time frame and carrying out of follow-up, influences the results reported. Likewise, the nature of the underlying data influences the results. Only population-based data is likely to be comparable. Institutional series always include selection bias. This was clearly seen in comparison of amputation rates as a measure of surgical outcome of CLI in hospital and population based data (Luther 1996)

6.6.2 Outcome

Amputation rates in CLI-patients depend on age, proportion of diabetes and degree of ischaemia. Before the era of arterial surgery, in a series of Juergens from the years 1939-1948 with non-diabetic patients younger than 60 years of age, 5-year amputation rates were reported to be 3.8 % for patients with rest pain or neuropathic pain and 19.8% for patients with ulcers or gangrene (Juergens 1960). In a series from the years 1947-1953 Boyd, Ratcliffe and Bloor assessed claudication patients (Bloor 1960, Boyd 1962). These patients were mainly treated conservatively or received nonreconstructive surgery (sympathectomies and tenotomies of the achilles tendon). In the first and third year after diagnosis critical leg ischaemia developed in 8.3% and 3.0% respectively, the deterioration being dependent on the age of the patient group. Of these critically ischaemic patients 23-57% required major amputation (*Table 8).*

Table 8: Amputation rates in CLI patients (Bloor 1960) with CLI determined clinically

Age	Mid-thigh amputations (annual% (average of 5 yrs))
35-44	38.4
45-54	23.3
55-64	42.0
65-74	41.0
75+	57.0

The amputation figures reported by Juergens are substantially lower than those reported by Bloor. The patient group in the studies was, however, different. Bloor included diabetic patients into his patient population, while Juergens excluded them. Additionally, Juergens' patients were all younger than 60. In Juergens' series it seems that only pulse palpation was used to establish the diagnosis of PAD, while Bloor used pulse palpations, walking tests and oscillometry in the diagnosis. All these factors may contribute to the differing amputation rates through differing patient populations.
In Bloor's material 4% of the original claudicants were diabetics, but he does not report the proportion of diabetics in the patient group developing CLI.

Table 9: Amputation incidences /million inhabitants

	Region	year	major amputations	minor amputations	BK/AK
Pohjolainen 1988*	Southern Finland	84-85	271	124	0.64
Lääperi 1993*	Southern Finland	89	200	59	0.58
Sayers 1993[£]	Leicestershire, GB	74-90	79	-	-
"	"	74	80	-	-
"	"	90	52	-	-
Luther 1994 [#]	Vaasa, Finland 70-74	137	-	0.53	
"	"	75-79	194	-	0.56
"	"	80-84	317	-	0.39
"	"	85-89	276	-	0.33
"	"	90-91	142	-	0.17
Pell 1994[#@]	Scotland, GB	90	142¤	-	-
Michaels 1994[#]	Oxford region, GB	?	149	-	1.76
Ebskov 1994 [#]	Denmark	83	345	-	-
"	"	90	250	-	-
Lindholt 1994*	Viborg, Denmark	86-87	409	-	0.75
"	"	89-90	309	-	0.87
Gutteridge 1994[&¤]	West Berkshire, GB	83-87	480	198	1.01
"	"	88-91	320	267	1.04
Trautner 1996		252			
Luther 1996*	Vaasa, Finland 80-91	274	-	0.27	
Karlström 1997[#]	Varberg, Sweden	85-88	342	-	2.89
"	"	89-92	274	-	1.99
Mattes 1997[#]	Western Australia	80-92	103[§]	-	-
Feinglass 2000[#¤]	Northern Illinois, US	93-97	208	-	1.16
Eskelinen 2004*	Southern Finland	2000	154		0.76

*= includes amputations both for vascular and other reasons
[#]= only vascular amputations
[&]= only vascular amputations (all amputations performed by an orthopaedic surgeon were excluded on the assumption that they were performed for other reasons)
[¤]= age adjusted incidences
[§]= population extrapolated
[£]= only amputations registered as PAD-amputations were included, amputations performed for diabetes without the PAD diagnosis were not included
[@]= only amputations registered as PAD-amputations were included

Other series assessing the outcome in patients unsuitable for revascularisation or with failed bypass attempts produced major amputation rates ranging between 32-50% at six months of follow-up (Klomp 1999, Norgren 1990, UK Severe Limb Ischaemia Study Group 1991). Only few studies have a follow-up longer than six months. In another study by Jivegård et al the amputation rate at 18 months was reported to be 54% and so was the major amputation rate at 2 years in the study by Klomp et al (Jivegård 1995, Klomp 1999).

In surgical series with vascular and endovascular treatment for critical leg ischaemia, major amputation rates ranging between 5 to 26% at 1 year and 14% to 49% at 2 years have been reported (*Table 10c*). In conservative and nonsurgical series major amputation rates ranged between 20% and 46% at one year (*Table 10a,b*).

Although the need for amputation is not imminent in all critically ischaemic patients, the general long-term outcome of critically ischaemic patients is quite poor. Mortality in this patient group is very high due to co-morbidities and cardiovascular manifestations of arterial disease (Hertzer 1984, Aronow 1994). In a study conducted in 1983 by Lassila et al the cumulative 10-year survival of CLI patients was 58% (Lassila 1986). Similarly, according to a recent review by Dormandy et al the one-year-mortality is approximately 20% while the 5-year mortality ranges somewhere between 40-70% (Dormandy 1999a).

In selected patients deemed unreconstructable, mortality rates between 11and 23 % have been reported after a follow-up of 6 months, while Jivegård reported a mortality of 30% after 18 months of follow-up (*Table 10a,b*).

In surgical series in-hospital mortality rates of 14% (Vascular Surgical Society of Great Britain and Ireland 1995), one-year mortality between 18 to 29% as well as mortality rates up to 88 % at 10 years have been reported (*Table 10c*).

Table 10a: Outcome of CLI (rest pain and ischaemic tissue loss): Conservative treatment

Author	patients	follow-up	major amp at follow-up	mortality at follow-up	dm	age [mean] (range)
Randomised studies with prostanoid treatment [CI] or epidural stimulation as treatment [CE] (here only the patients with placebo or conservative treatment included)						
Belch 1983 [CI](FIII+IV)	13	6 mo	0	3 (23%)	0	69
Norgren 1990 [CI](FIV)	53	6 mo	24(45%)	8 (15%)	18 (34%)	-
UKslisg¤1991[CI](FIII+IV)	71	2 weeks	21(30%)	2 (3%)	35 (49%)	73 (37-89)
“	“	3 mo	27(39%)	7 (10%)	“	“
“	“	6 mo	33(47%)	8 (11%)	“	“
Jivegård 1995 [CE](FIII+IV)	26	18 mo	14(54%)	8 (30%)	5 (19%)	[73]
Klomp 1999 [CE](FIII+FIV)	60	6 mo	18(32%)	9 (15%)	23(38%)	72
“	“	2 yrs	29(54%)	41(68%)	“	“
Amann 2003 [CE] [FIII+FIV]	39	1 yr	18(46%)	0	(31.7%)§	[68](37-88)§

*=median, ¤=UK severe limb ischaemia study group, # =number of procedures, not pts, §=Patient demographics of the whole patient population
F= Fontaine classification

Table 10b: Outcome of CLI (rest pain and ischaemic tissue loss): Non-reconstructive treatment

Author	patients	follow-up	major amp at follow-up	mortality at follow-up	dm	age [mean] (range)
Randomised studies with prostanoid treatment [CI] or epidural stimulation as treatment [CE] (here only the patients WITH prostanoid and epidural stimulation treatment included)						
Belch 1983 [CI](FIII+IV)	13	6 mo	0	3 (23%)	0	69
Norgren 1990 [CI](FIV)	50	6 mo	16(32%)	5 (10%)	15 (30%)	-
UKslisg¤1991[CI](FIII+IV)	80	2 weeks	15(21%)	2 (3%)	25(31%)	73 (33-89)
“	“	3 mo	19(26%)	3 (4%)	“	“
”	“	6 mo	23(31%)	4 (5%)	“	“
Jivegård 1995 [CE](FIII+IV)	25	18 mo	9 (36%)	8 (30%)	5 (19%)	[73]
Klomp 1999 [CE](FIII+FIV)	60	6 mo	19(34%)	9 (15%)	22(37%)	[73]
“	“	2 yrs	25(48%)	39(65%)	“	“
Jacobs 1990 [E] [FIII+FIV]	20	immediate	2 (10%)	0	7 (35%)	[72](52-84)
“	“	1yr	(20%)	“	“	“
“	“	2 yrs	(44%)	“	“	“
Amann 2003 [CE] [FIII+FIV]	73	1 yr	21(29%)	0	(31.7%)§	[68](37-88)§

*=median, ¤=UK severe limb ischaemia study group, #= number of procedures, not pts, §=Patient demograpics of the whole patient population
F=Fontaine classification

Table 10c: Outcome of CLI (rest pain and ischaemic tissue loss): vascular surgical series

Author	patients (legs)	follow-up (median)	primary amputation	reconstr or pta	major amp at follow-up[a]	mortality at follow-up	dm	age[mean] (range)
Surgical series (with either all pts with reconstructive procedures [S] or some treated conservatively as well [S+C])								
DeWeese1971 [S]	61(67)	5 yrs	0	100%	24 (36%)	38 (62%)	25 (25%)	(29-87)
DeWeese 1977 [S]	61(67)	10 yrs	0	100%	25 (37%)	54 (88%)	25 (25%)	(29-87)
Veith 1981 [S] 755	5 yrs	76(10%)	679(90%)	-	(52%)[@]	(>60%)	[70]	
"	"	1 mo	"	"	152 (20%)	29(4%)	"	"
Lassila 1986 [S+C]	84	10 yrs	-	-	-	64(76%)	-	-
Wolfe 1986 [S+C]	409(429)	1 yr	17%	61%	26%	18%	-	-
Griffith 1988 [S]	402	2 yrs	148	260(65%)	197(49%)	54 (21%)[@]	-	73* (37-87)
"	"	1 mo	"	"	-	(9%)	-	"
Hickey 1991 [S]	315(329)	8-68 mo	45	315(88%)	-	41% 5yrs[©]	76 (24%)	[73] (46-93)
"	"	1mo	"	"	-	(7%)	"	"
Taylor 1991 [S]	498(627)	1-114 mo[$]	14(2%)	484(613 legs)	55(9%)	146 (30%)[@]	212(43%)	[68](24-97)
"	"	1yr	"	" (97%)	32(5%)	71(15%)[@]	"	"
"	"	2yss	"	"	37(6%)	96(20%)[@]	"	"
"	"	5yrs	"	"	51(8%)	146(30%)[@]	"	"
VSSGBI[§] 1995[S+C]	679	on discharge	107(16%)	427(63%)	146(22%)	92 (14%)	204(30%)	-
Luther 1996b [S]	(151)	1 yr	0	100%	13%	17%	39%	[69]
"	"	3 yrs	"	"	18%	-		
"	"	5 yrs	"	"	23%	52%		
ICAI 1997 [S+C]	522	2 yrs	49(9%)	232(44%)	72(14%)	165(32%)	157(30%)	71*
Luther 1997a [S]	99(109)	1 mo	0	100%	14(13%)	4 (4%)	81 (74%)	75*
"	"	1yr	"	"	-	20%[©]	"	"
"	"	2yrs	"	"	-	31%[©]	"	"
"	"	3yrs	"	"	-	46%[©]	"	"
Luther 1997b [S]	188 (209)	1 yr	0	100%	19%[£]	33 / 5%[Θ]	89(47%)	-
"	"	3 yrs	"	"	24%[£]	55 / 20%[Θ]	"	-
"	"	5 yrs	"	"	29%[£]	58 / 29%[Θ]	"	-
Holdsworth 1997[S+C]	319(436[e])	12 mo	78(18%)	187(43%)	-	127(29%)	115(26%)	[73]
Kantonen 1998 [S]	1761[#]	1 mo	0	100%	7,5%	4,7%	41%	[70,5]
Luther 1997c [S]	117	1 mo	51(44%)	66(56%)	-	16 (14%)	62 (53%)	81/75*[%]
"	"	1 yr	"	"	-	35 (30%)		
"	"	2 yrs	"	"	-	45 (38%)		
"	"	3 yrs	"	"	-	60 (51%)		
"	"	5 yrs	"	"	-	76 (65%)		
Biancari 2000 [S]	62 (66)	1 mo	0	100%	3%	-	52(79%)	[67](63-93)
"	"	1 yr	"	"	12%	-	"	"
"	"	2yrs	"	"	12%	28%	"	"
Van Damme 2003 [S]	81(90) °	5 yrs	0 (28amp)	100%	11%	33%	35 (43%)	[70](37-93)
Bailey 2003 [S+C]	129(130)	3-15 mo (9)	11(7%)	62[#]	17(13%)	39 (27%)	39 (30%)	81*(31-98)
Vayssariat 2004 [S+C]	57	1,5-49mo (20)	1 (2%)	35(61%)	10 (18%)	25 (44%)	23 (40%)	76(43-96)

[©] = cumulative data (mortality or amputation)
[@]=mortality of operated (bypass) pts only
-= information not available
*=median age
[¤]=UK severe limb ischaemia study group,
[#]= number of procedures, not pts,
[§]=Vascular Surgical Society of Great Britain and Ireland
[$]=mean 21 months
[a]=major amputation at follow-up: both primary amputations and secondary amputations
[%]=median age of primarily amputated pts/ median age of reconstructed pts
[£]=only autogneous vein bypass procedures, prosthetic grafts excluded
[Θ]=mortality diabetics / non diabetics
[e]= admissions
[°]= includes 4 cases with claudication

Table 11a: Patients alive with leg: Conservative or non-reconstructive series
Randomised studies with prostanoid treatment [CI] or epidural stimulation as treatment [CE]

Author	patients	follow-up	alive with leg at follow-up	dm	mean age (range)
Klomp 1999 [CE](FIII+FIV)	120	2 yrs	(27%)	32 (27%)	
UKslisg¤1991[CI](FIII+IV)	71	6 mo	(30%)	35 (49%)	73 (37-89)
UKslisg¤1991[CI](FIII+IV)	80	6 mo	(49%)	25 (31%)	73 (33-89)

Table 11b: Patients alive with leg: Vascular surgical series

Author	patients	dm	[mean] age (range)	alive with leg at 1 year	alive with leg at 2 years
Veith 1981 [S]	755	(>60%)	[70]	(68%)	(54%)
Griffith 1988 [S]	208	-	73* (37-87)	152 (73%)	137(65%)
Hickey 1991 [S]	315(329)	76 (24%)	[73] (46-93)	212 (64%)	177(54%)
Luther 1997a [S]	99(109)	81 (74%)	75*	50 (50%)	20 (20%)
Biancari 2000 [S]	62 (66)	52 (79%)	[67] (63-93)	(70%)	(66%)

*median age

As the both amputation risk and mortality are high in critically ischaemic patients, the proportion to survive with a viable limb will be relatively small. In an Iloprost study from the UK, 42% of the conservatively treated patients were alive with an intact leg at 6 months, while in Klomp's study 57% survived with an intact leg at 6 months (Klomp 1999, UK severe limb ischaemia study group 1991). The proportion retaining the leg and surviving for 2 years was 34% in the latter study (Klomp 1999).

Although data of different series are not directly comparable and no recent data concerning the true natural outcome of critically ischaemic patients exist, the bleak prognosis for these patients seems evident.

7. AIMS OF THE PRESENT STUDY

The main aim of this study was to investigate how well the legs at risk to be amputated due to critical leg ischaemia can be identified and what their outcome on population basis is.

The specific aims were to assess:
1) The accuracy of ankle brachial index measurements in CLI
2) The usefulness of ABI-measurements in leg viability evaluation
3) To assess the proportion of IC preceding CLI
4) The natural outcome of critical leg ischaemia
5) The mode of organising vascular surgical service and the need of major amputations in Uusimaa

8. MATERIAL AND METHODS

All of the studies included critically ischaemic patients either from the Department of Vascular Surgery at the Helsinki University Central Hospital or its catchment area. The patients were critically ischaemic according to the Fontaine classification. Some fulfilled the additional pressure criteria of the Second European Consensus Document. All in all 42% of the patients investigated in the Vascular Surgical Department were diabetics, partly owing to the fact, that the treatment of critically ischaemic patients with additional risk factors such as diabetes was concentrated to the Helsinki University Hospital. The population based study V relied mostly on registry data, which made the assessment of possible diabetes and pressures impossible. The ethical committee approved all studies. In the studies I and III informed consent was obtained from each patient participating in the study. The patient characteristics in the different studies are summarised in *Table 12*.

Table 12: patient characteristics in the different studies

Study	I	II	III	IV	V
No of pts	55	110	100	105	1243
Males	31	51	60	47	609
Females	24	59	40	58	634
Diabetics	12	56	44	53	NA
Rest pain	100%	61%	83%	63%	100%
Ulcer		63%	70%	61%	
Gangrene		18%	37%	18%	
Previous amputation#	0%	5%	7%	6%	
Mean ABI [median]	0.37[0.39]&	0.30[0.31]	0.55[0.43]&	0.34[0.31]&	NA
ABI-range	0-1.44&	0.3-0.47	0-1.77&	0-2.28&	NA
Eur cons doc*	100%	95%	82%	100%	NA
TASC	100%	100%	100%	100%	NA

*patients complying with the European consensus document criteria for CLI
&= pseudohypertensive pressure values not excluded
#= previous major amputations

Study I: Reproducibility of ABI measurements

In order to assess the accuracy and repeatability of pressure measurements in critical leg ischaemia, the pressure measurements were performed in a situation resembling the widespread clinical practice in this country. The pressures of 19 consecutive patients with 22 critically ischaemic legs were measured by 4-7 different measurers (part A). The measurers had variable experience in performing measurements and the patients were all measured on the ward while they were waiting for angiography, consultation or operative treatment. The measurers had ample time for their measurements and the occluding cuffs were already in place. All measurements were performed using a CW-Doppler with earphones (9,5 MHz, model 806-CB Parks Medical Electronics, Oregon, United States) and the measurement variability of ankle brachial indices was calculated. To compare the results, a second subset of 30 patients with 33 legs was included into the study and measured by two experienced vascular technicians (part B) and the inter-observer agreement calculated. Patients with incompressible arteries were excluded, as were patients who had large ulcers at the site of the cuff precluding repeated pressure measurements.

Study II: Predictive value of pressure measurements

The pressure measurements and ABI-values of 110 critically ischaemic patients with 145 critically ischaemic legs measured at admission, were assessed. These patients had been excluded from operative treatment due to technical reasons or increased operative risk in the years 1988-1993. The positive and negative predictive values of the pressure measurements were calculated in terms of amputation risk within 3 months of admission. In order to assess the influence of changing treatment policies throughout time, the patients were divided into two groups and analysed separately: the ones having attended the vascular outpatient clinic in the years 1988-1990 and those in the years 1991-1993.

Study III: The proportion of claudication prior to CLI

In order to assess the course and development of critical leg ischaemia, 100 patients were included into the study. They had been referred to the vascular surgical outpatient clinic. Most patients fulfilled the criteria for critical leg ischaemia according to the European Consensus Document, which were rest pain, ulceration or gangrene together with ankle pressures $\leq$50 mmHg or toe pressures $\leq$30 mmHg. Some additional patients were included if they presented with an ulceration or gangrene together with ankle-brachial indices $\leq$ 0.5 or toe-brachial indices $\leq$0.2 (Ramsey 1983). All of these patients were interviewed to assess the presence of claudication symptoms before developing symptoms of CLI. The interviewer filled in an additional questionnaire. The questionnaire was focused on the order of appearance of the various symptoms of PAD, their treatment and duration (appendix I). Special attention was paid to the presence of conditions preventing the patient to experience claudication pain. The influence of diabetes was assessed as well as the distribution of different symptoms.

To analyse the potential bias affecting the outcome by treatment delay, a subset of 68 CLI-patients was analysed separately to assess the effect of treatment delay on the amputation risk. In these patients the referring physician suspected critical leg ischaemia to be the underlying cause for the symptoms. Proper vascular laboratory assessment with toe pressure measurements, Doppler-measurements from each ankle vessel and pulse volume recordings were carried out. A vascular surgeon clinically evaluated the patients. The length of the time period in which the symptoms indicating CLI had been present, was

calculated and the association with amputations within 1 year was assessed using the Students *t*-test for comparison of means.

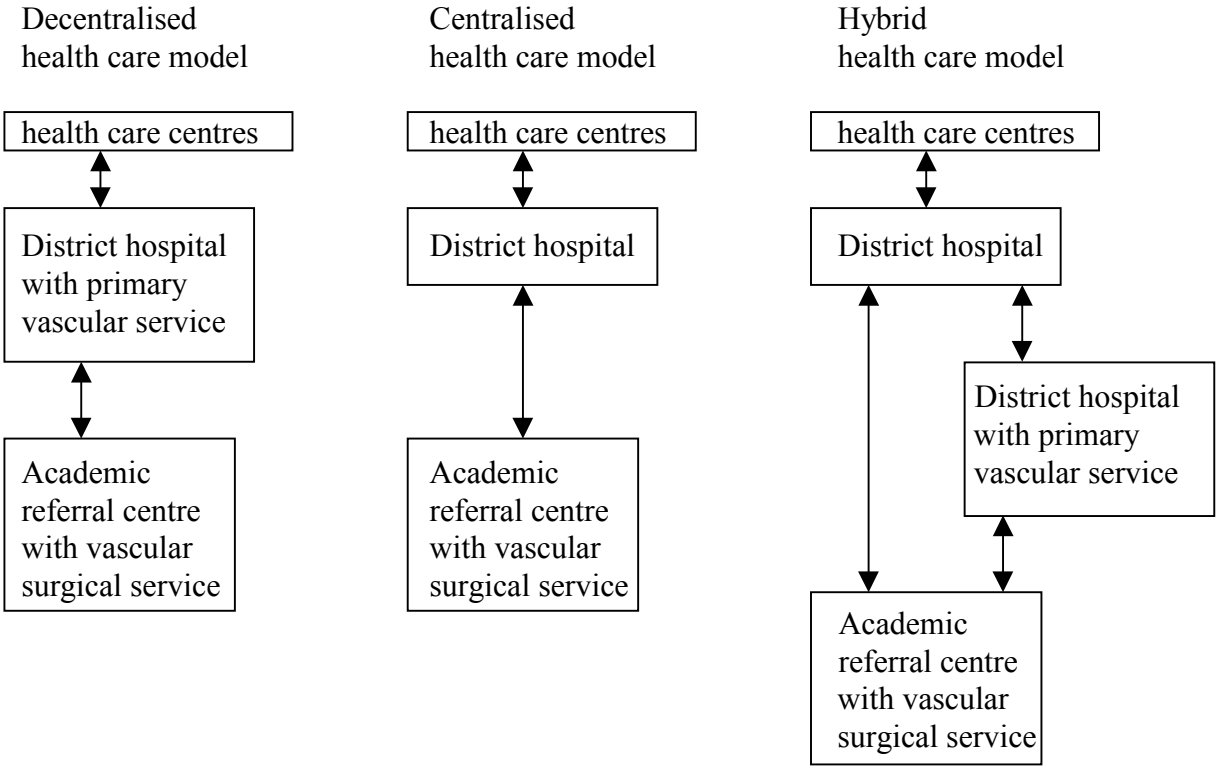
Study IV: Outcome of unreconstructed CLI

105 patients with critical leg ischaemia according to the European Consensus Document had been considered unsuitable for reconstructive procedures, either due to technical reasons or in combination with increased operative risk. Technical reasons precluding operative treatment included occlusive lesions extending well below the distal poplitea, as femoropedal bypass procedures were not performed at that time. Also, the need of extensive surgery together with a high operative risk was among the exclusion criteria. All in all 54% of the patients had been excluded from operative treatment due to technical reasons alone, or in combination with an increased operative risk, and 33% due to an increased operative risk alone. The remaining 6% were excluded due to their refusal. The one-year-outcome was assessed retrospectively by tracing down their hospital records from different hospitals, as well as their records in local health care centres. The eventual amputation date as well as the amputation levels was recorded. Similarly, in case of death, copies of death certificates were obtained from the Finnish Statistical Office and the cause and date of death recorded. Survival analyses in terms of leg survival, patient survival and survival with leg were made.

Study V: Comparison of vascular surgical service models

An analysis of the treatment efficacy and outcome of critical leg ischaemia was performed in the hospital district of Uusimaa in the years 1991-1997. The population in the hospital district was 702 260 at the beginning of the study period and 800 640 at the end. All information on vascular surgical operations, amputations and subsequent care performed during that period was extracted from the hospital discharge register kept by the National Research and Development Centre for Welfare and Health. Reliable data on endovascular procedures was not uniformly available and was therefore omitted. The patients having been treated for critical leg ischaemia were identified using the nationwide register for vascular surgical procedures, Finnvasc. At the end of the time period, one of the participating hospitals had ceased to report its cases into the Finnvasc database. Its hospital records on vascular surgical procedures performed in the years 1996-1997 had to be reviewed by the investigators in order to identify all critically ischaemic patients in the region. The identification of patients with primary amputation, as well as follow-up data concerning hospital care and care in other institutions, was provided from the hospital discharge register. The different municipalities, in which the patients were registered, were divided according to their referral system in three different groups: a centralised system, a decentralised system and a hybrid system (*Fig 7*). Age- and sex-adjusted incidences were calculated for major amputations, hospital days, mortality and femorodistal bypasses.

Figure 7: Vascular surgical service models



To evaluate the effect of differing socio-economic features of the population on CLI- and amputation incidences, the differences between the municipalities included into the study were assessed. Poisson regression analyses were carried out.

9. RESULTS

Study I: Reproducibility of ABI measurements

ABI measurements performed by experienced vascular nurses in appropriate surroundings did not differ from each other by more than 0.14. The mean coefficient of variation was found to be 3.15. In contrast to this, measurements performed in surroundings resembling the situation in many hospitals by measurers with variable experience showed a mean coefficient of variation of 56.1. 19% of the ABI values differed more than 0.15 and 28% more than 0.10 from the mean ABI.

Study II: Predictive value of pressure measurements

After a follow-up-period of three months 36 (25%) legs had been amputated either at thigh or calf level. Of the patients having rest pain, i.e. Fontaine III 16% were amputated, whereas of patients having ischaemic tissue loss, i.e. Fontaine IV 28% were amputated (NS). Neither did the result of those legs having only low ankle pressures (amputation rate 25%) differ significantly from those who had both low ankle and toe pressures (amputation rate 37%). Only isolated acral ischaemia was connected to a better leg salvage: 11% were amputated if only the toe pressure indicated CLI ($p < 0.025$).

Although the pressure ranges were almost identical in the amputated and nonamputated group (*Table 13*), there were significant differences in ankle pressures ($p = 0.01$), toe pressures ($p = 0.02$) as well as ABI ($p = 0.009$) between the amputated and nonamputated group (*Figures 8-10*)

Figure 8: Frequencies of measured ankle pressures (mmHg)

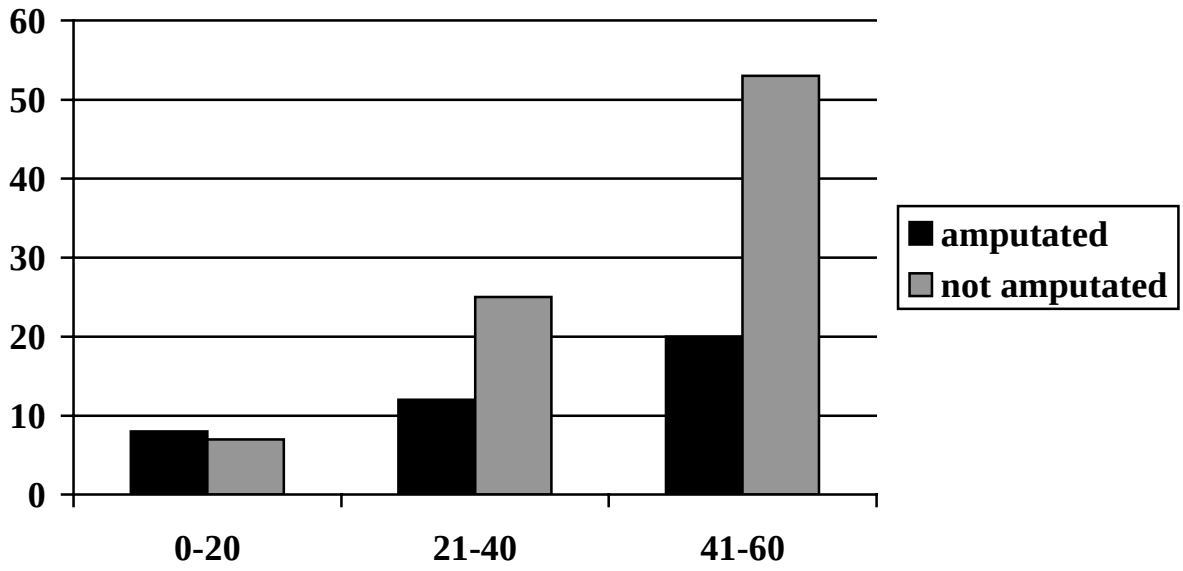


Figure 9: Frequencies of measured toe pressures (mmHg)

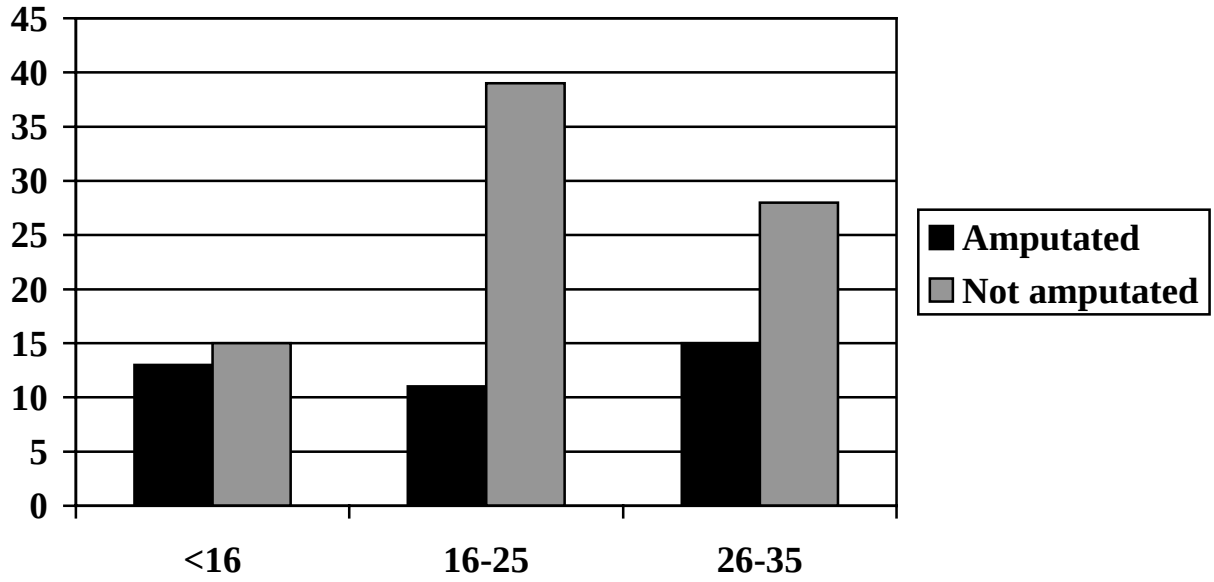
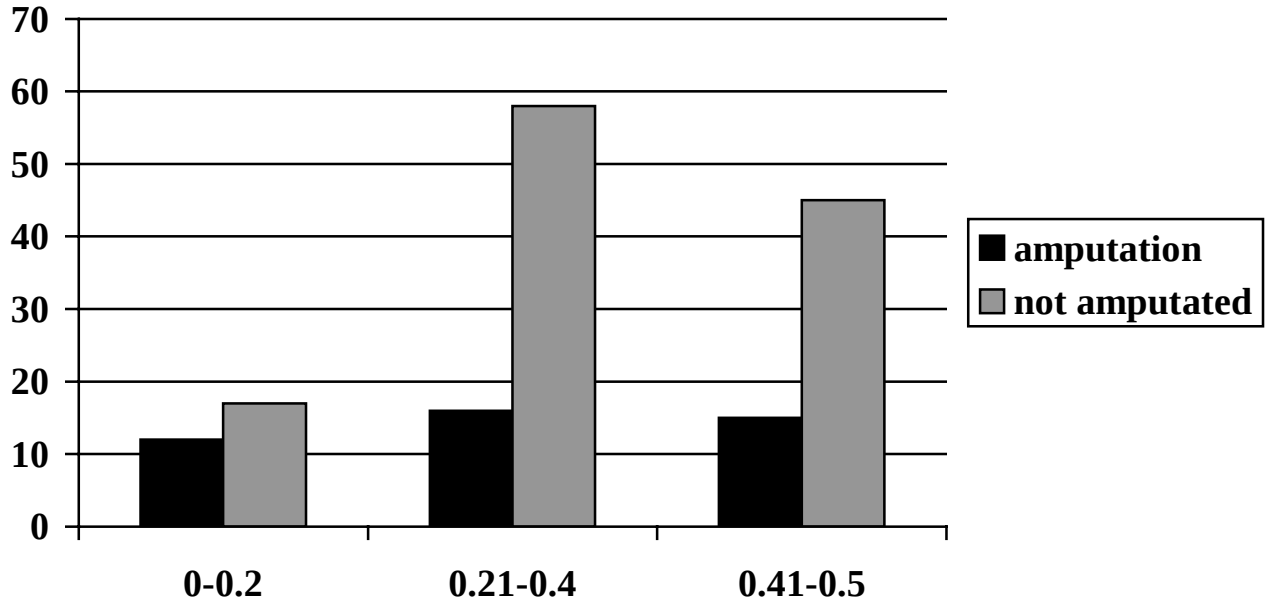


Figure 10: Frequencies of measured ankle brachial pressure indices



There were, however, no clear cut-off levels for pressure values indicating risk for major amputation (*Tables 14a-c*).

Table 13: Pressures in the amputated and nonamputated groups

	Major amputation			No major amputation			Significance
	Mean	Median	Range	Mean	Median	Range	
Ankle pressures	32	34	0-56	42	45	0-59	$p<0.05$
Toe pressures	16	17	0-30	20	20	0-30	$p<0.05$
ABI	0.26	0.24	0.03-0.47	0.31	0.32	0.1-0.5	$p<0.01$

Table 14a: Predictive values of ankle pressure in terms of amputation at three months

Ankle pressures	<30	<40	<50	<60
Sensitivity	0.31	0.5	0.67	0.89
Specificity	0.93	0.78	0.57	0.28
PPV	0.58	0.43	0.34	0.29
NPV	0.8	0.83	0.84	0.89
Overall accuracy	0.77	0.71	0.59	0.43

Table 14b: Predictive value of toe pressures in terms of amputation at three months

Toe pressures	<10	<20	<30
Sensitivity	0.14	0.5	0.93
Specificity	0.93	0.77	0.16
PPV	0.40	0.42	0.28
NPV	0.76	0.82	0.87
Overall accuracy	0.72	0.70	0.36

Table 14c: Predictive value of ankle brachial indices in terms of amputation at three months

ABI	<0.3	<0.4	<0.5
Sensitivity	0.57	0.8	0.94
Specificity	0.61	0.37	0.18
PPV	0.32	0.29	0.27
NPV	0.81	0.85	0.91
Overall accuracy	0.60	0.47	0.37

PPV = positive predictive value
NPV= negative predictive value

At any level of pressure whether measured on toe or ankle level either sensitivity or specificity was poor in predicting amputation. Neither could any difference in Fontaine-classification, mean pressure values or the age of the patients be seen.

Study III: The proportion of claudication prior to CLI

Sixty-three patients out of 100 had experienced symptoms of claudication prior to developing CLI. Twelve of them reported that the claudication symptoms had been relieved before developing symptoms of CLI. Six of them had had previous endovascular or surgical reconstructive procedures whereas the other six did not walk enough to develop claudication.

Thirty-seven patients had CLI as the initial symptom of peripheral arterial disease. CLI developed after a small trauma (26 patients), through gradually increasing pain and subsequent ulceration or gangrene (8 patients), or gangrene of the toe without prodromal signs of occlusive arterial disease (3 patients). 20 patients without earlier signs of PAD (54%) had diabetes, four of which with previously diagnosed neuropathy, whereas 38% of those with previous sings of PAD had diabetes, none with known neuropathy.

The patient groups did not differ from each other in terms of age, diabetes, coronary heart disease, hypertension, cerebrovascular disease, renal disease, previous reconstructive procedures or current smoking habits (*Table 15*). In terms of recent smoking, non-smoking, diabetes and the distribution of rest pain or ulcers the two groups did differ. Patients with previous claudication had a greater proportion with recent smoking and a lower proportion of non-smokers than the patient group without previous claudication. Diabetes was less common in the group with previous claudication, and so was the presence of ulcers. Rest pain was in contrast more common in the group with preceding claudication (*Table 15*).

Table 15: Patient characteristics of 100 interviewed patients

	Previous claudication	no previous claudication	p-values
Number of patients	63	37	
Current claudication	51	0	
Male/female (%)	(65/35)	(51/49)	0.17
Mean age	71	72	0.62
Current smoker	17 (27)	10 (27)	0.99
Recent smoker (cessation< 5yrs)	14 (22)	1 (3)	0.008
Ex-smoker (cessation< 5yrs)	14 (22)	8 (22)	0.94
Non-smoker	18 (29)	18 (49)	0.043
Diabetes	24 (38)	20 (54)	0.12
Rest pain	58 (92)	25 (68)	0.016
Ulcer	37 (59)	33 (89)	0.013
Gangrene	24 (38)	13 (35)	0.76
Pressures: mean [median]{range}			
Ankle*	66 [59]{0-202}	103 [90] {37-197}	
Toe	15 [0] {0-78}	22 [15] {0-117}	

( ) = percentage within the group
* = pseudohypertensive pressures excluded

Six patients with acute-on-chronic-ischaemia could be identified in those patients with earlier symptoms of PAD. Of the patients with acute on chronic ischaemia, three had undergone previous reconstruction and two of these did not have claudication anymore.

Nineteen of the previously asymptomatic patients (12 nondiabetics and 7 diabetics) did not walk enough to develop symptoms of claudication. In 14 of these, other disorders, such as hemiparesis, arthrosis, cardiac failure etc. were observed as the cause for limited ambulation, whereas five patients presented with no obvious reason for limited exercise or the awareness of any factor restricting their walking. In five additional patients the reason for not developing claudication remained unclear; they did not declare to have very limited ambulation nor were there any co-morbidities or a sudden onset of pain explaining the absence of previous symptoms.

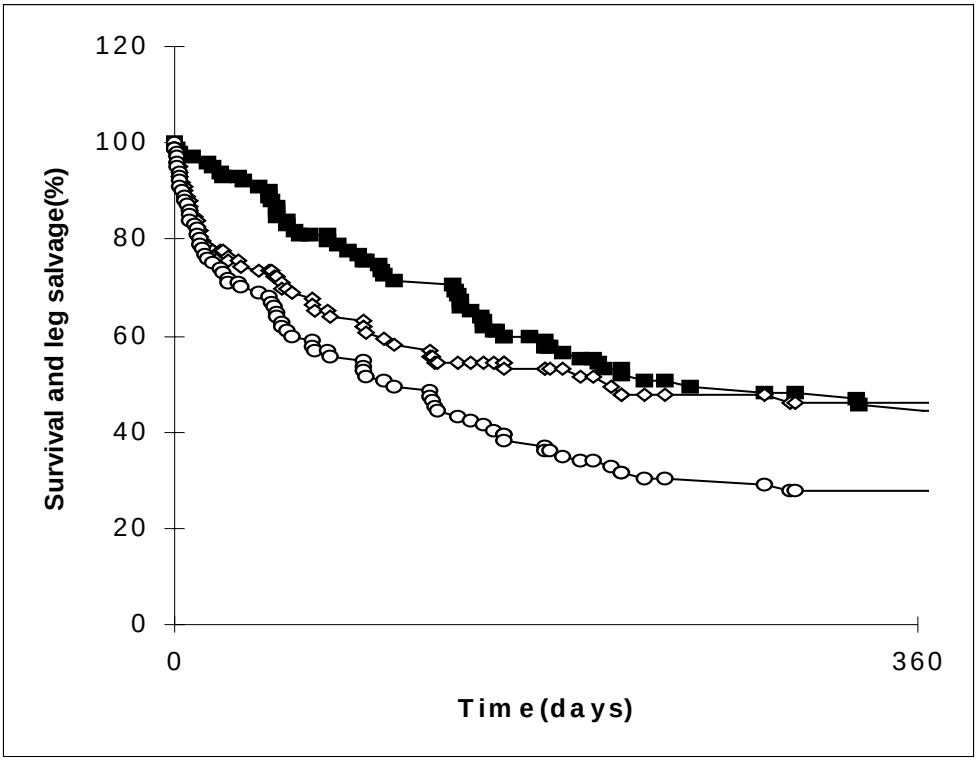
In the subgroup of 82 patients with pressure defined CLI there were 32 patients (39 %). In the subgroup of 18 patients with index defined CLI, five patients (28 %) had never experienced claudication. In the former subgroup 23 patients (5 with and 18 without previous claudication) and in the latter subgroup two patients (1 with and 1 without previous claudication) did not move enough to develop claudication. The symptoms of claudication had been relieved due to previous reconstructive procedures in three patients in each subgroup. There were no significant differences in the patient characteristics between the two subgroups. Only a tendency towards a larger proportion of non-smokers among the patients without claudication could be seen. (p=0.054)

In the additional subset analysis of 68 patients with CLI-suspicion at their first admission to the vascular outpatient clinic and subsequent interview with vascular assessment, 3 patients were not considered to have vascular disease severe enough to account for the symptoms indicating CLI. The symptoms were regarded as caused by other disorders than vascular disease and they were excluded from the study. In the remaining 65 patients the time period between the first notion of pain or tissue loss due to CLI and the arrival at the vascular outpatient clinic ranged from 1 day to 12 months. Twelve patients underwent a major amputation within one year after presentation. The mean duration of CLI-symptoms was 109 days (SD 88.9) (range 1 day to 12 months) in the patients without amputation and 89 days (SD 98.7) (range 30 days to 12 months) with amputation. No significant difference between these could be detected (p=0.516). Furthermore, there was no difference between the treatment delays of various groups.

Study IV: Outcome of unreconstructed CLI

Of all 136 legs with critical leg ischaemia according to European criteria 81% were saved at one month, 70% at 3 months, 58% at 6 months and 54% at 1 year. Five patients were lost to follow-up during the first month and further six were lost up to 1 year. Both mortality and amputation rates were high in the study population (*Figure 11*). 72% of the patients deceased, died of cardiovascular reasons. Of all 105 patients 93%, 77% and 46% were alive at 1, 3, and 12 months, respectively. The 1 year survival of an age and sex adjusted population would have been 93%. A favourable outcome was observed in 71%, 51% and 28% of the patients, who were alive and not amputated at 1, 3 and 12 months (*Figure. 9*).

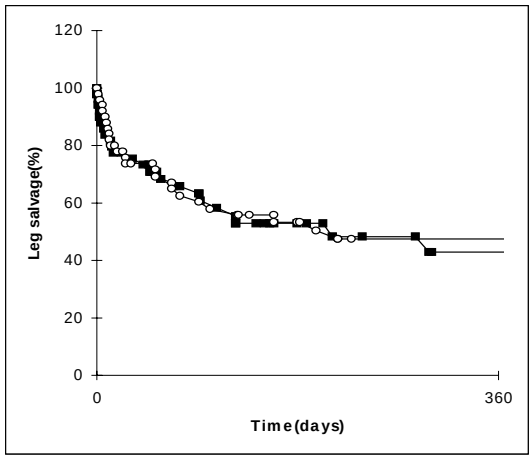
Figure 11: Patientwise survival and leg preservation

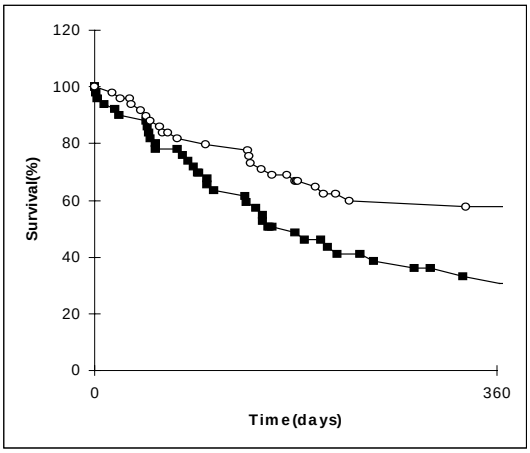


Survival (-■-), Preservation of the leg (-◊-), Survival preserving the leg (-○-)

Diabetics were found to fare worse than nondiabetics in terms of survival (p<0.01) (*Figure 12a*), but not in terms of preserving the leg (*Figure 12b*).

Figure 12: The association between diabetes and a) leg preservation and b) patient survival



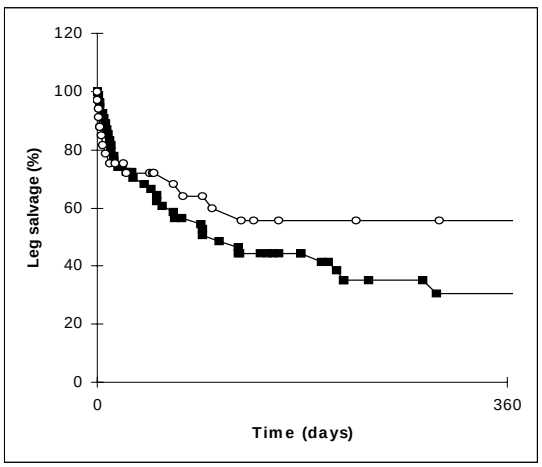


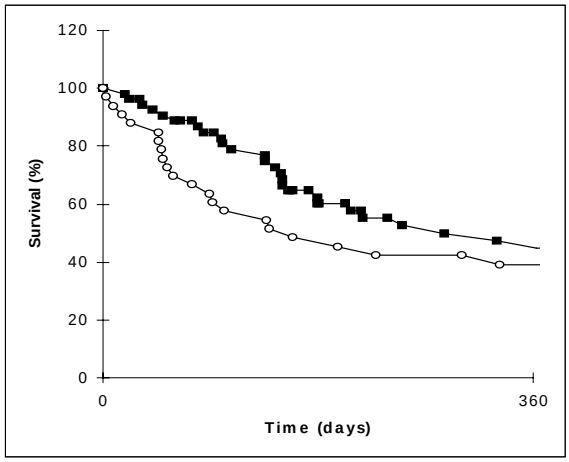
Diabetics (-■-); Nondiabetics (-○-)

Patients with bilateral CLI had a worse prognosis for survival (p<0.01) and leg preservation (p<0.05) than those with a unilateral CLI at presentation.

If the operation was rejected due to technical reasons alone or in combination with a high operative risk, preserving the leg and patient survival were the same as in patients rejected solely for high operative risk (NS) (*Figures 13a,b*).

Figure 13: The association between the reason for being excluded from operative treatment and a) preserving the leg and b) survival: technical reason (-■-), high operative risk (-○-)

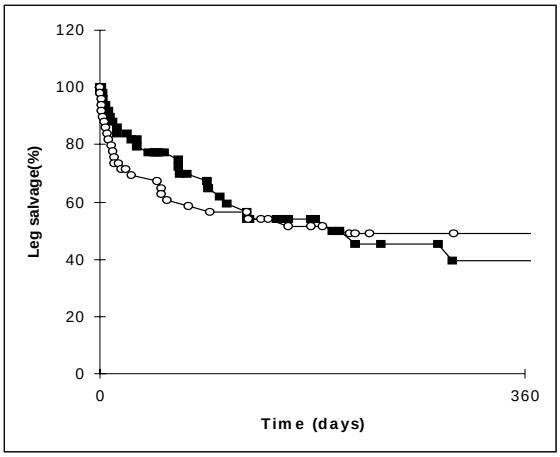




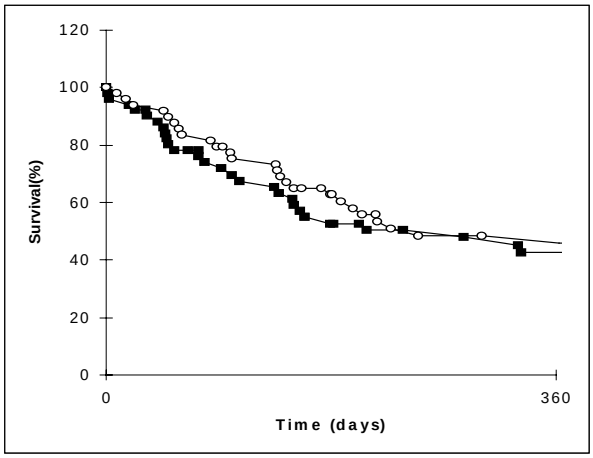
Three of the seven patients with a clinically borderline CLI deceased during the study year although none of them lost their leg. Of the six patients, who refused operative treatment three died and one was amputated in within one year. Known coronary heart disease did not significantly affect the outcome of limb salvage or survival rate (*Figure 14 a,b*).

Figure 14: The association between known coronary heart disease and a) preserving the leg (NS) and b) survival (NS)

a)



b)



CHD (-■-), no CHD (-○-)

Study V: Comparison of vascular surgical service models

1 243 patients with critical leg ischaemia were identified in the years 1991-1997. After the diagnosis of critical leg ischaemia they had 2 993 in-patient hospital stays in all, during which they spent 65 289 days in hospital.

During the study period 732 patients were amputated at calf or thigh level, all in all 967 major amputations were performed. The mean annual major amputation incidence was 136 per million inhabitants.

As the intention was to assess the development through the years, age- and sex-standardised major amputation annual incidences within one year of the diagnosis were calculated. The major amputation incidences showed considerable annual variation (*Figure 15*), although with a visible overall tendency of declining with the years (*Table 16, Figure 16*).

Figure 15: Annual age and Sex standardised amputation incidences within one year of diagnosis (/ 100 000 inhabitants aged 40 years and older)

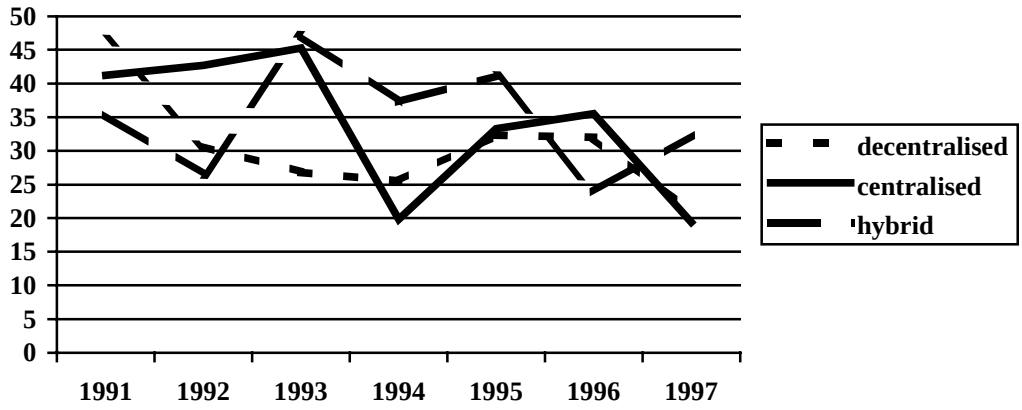


Figure 16: Annual age standardised major amputation incidences in Uusimaa (/100 000 inhabitants) (in a population of 40 years and older)

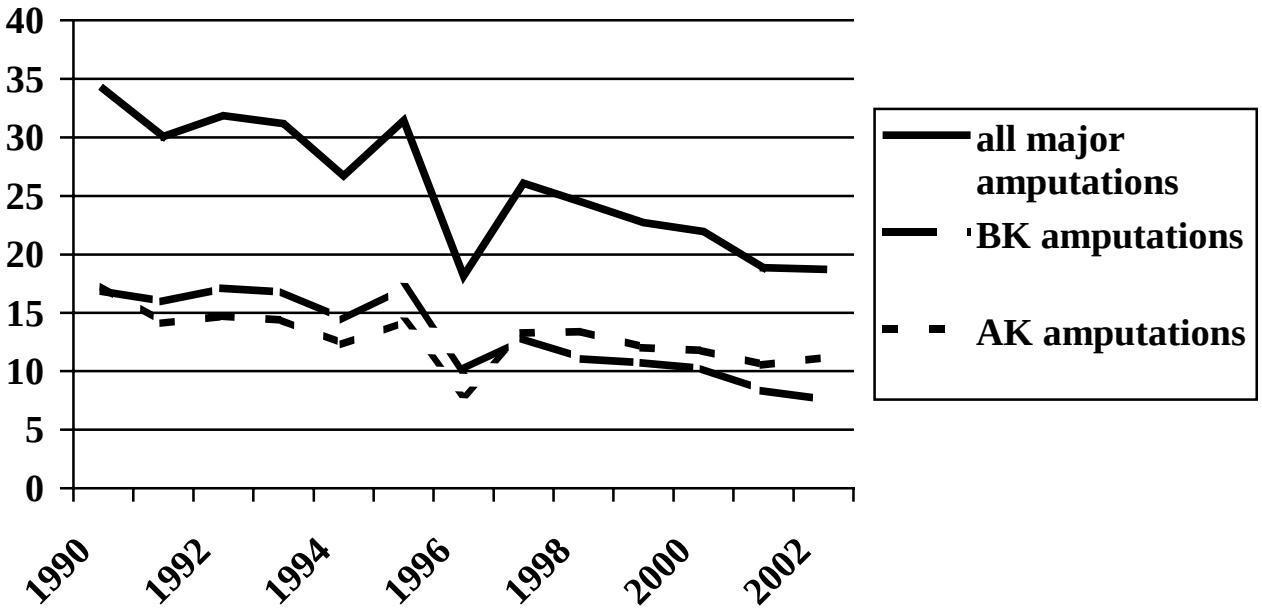


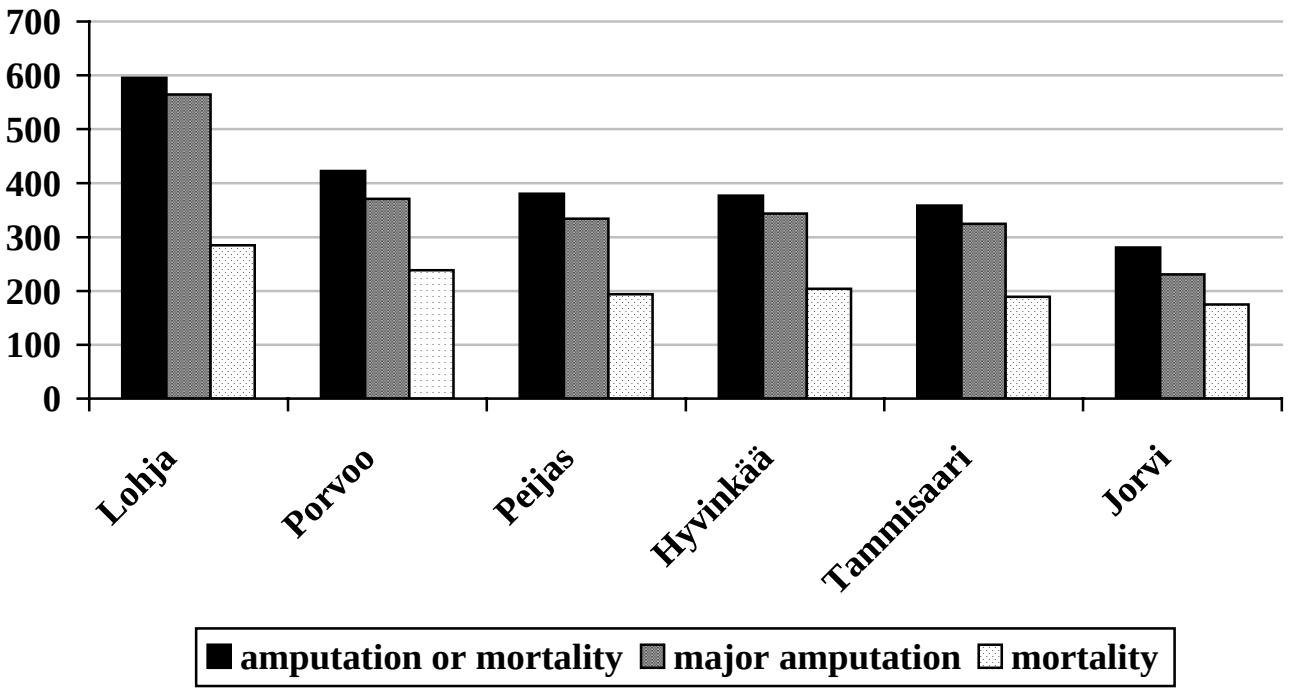
Table 16: Major amputations in the Uusimaa Hospital District

Year	Amputated patients	incidence* in the total population
1991	124	167
1992	105	139
1993	120	157
1994	88	113
1995	116	148
1996	102	129
1997	77	96

*= incidence of amputated patients / million inhabitants

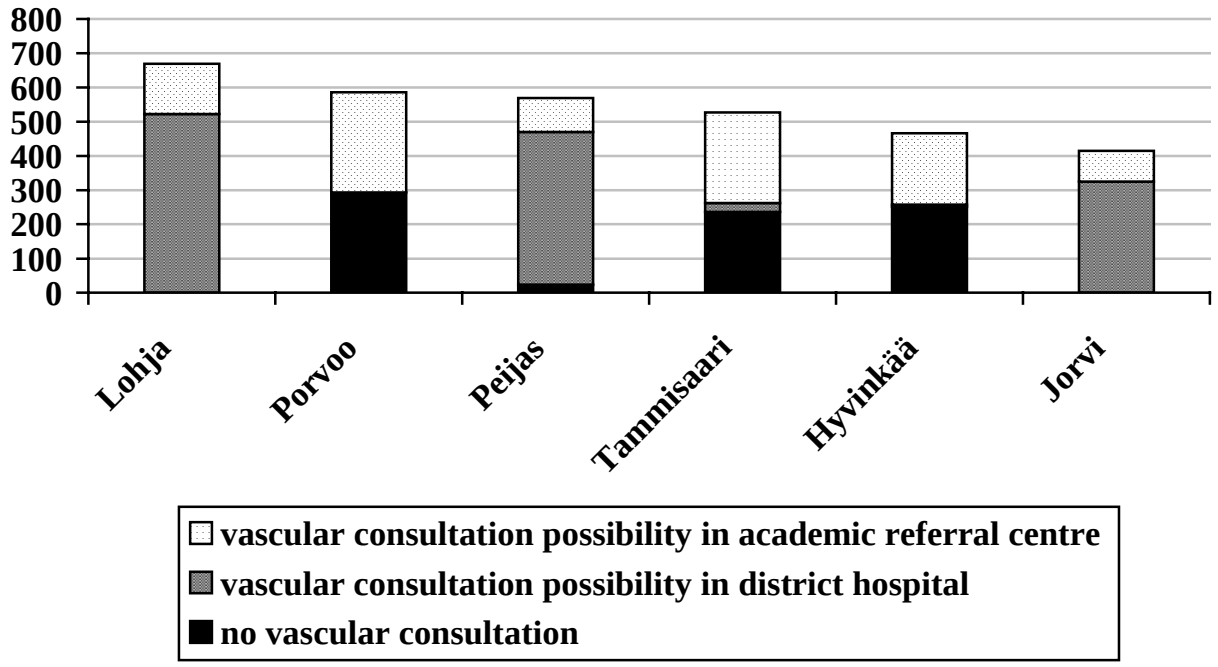
No difference in major amputation incidences between the different service models could be detected. Therefore the following incidence calculations were made on the basis of hospital subdistricts. Age and sex-standardised incidences on mortality (*Figure 17*), major amputations (*Figure 17*), vascular procedures and hospital utilisation showed considerable differences within the referral models (Lohja, Jorvi and Peijas = decentralised model; Porvoo and Tammisaari = centralised model; Hyvinkää = hybrid model).

Figure 17: Major amputations and mortality in the different hospital subdistricts within one year after diagnosis (age- and sex standardised incidences /100 000 aged 40 and over)



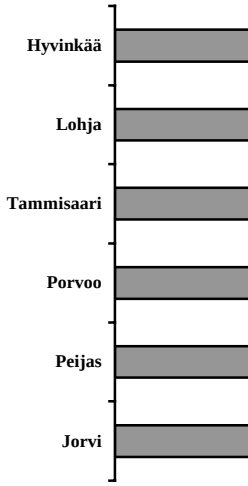
When calculating age and sex-standardised incidences of critical leg ischaemia within every of the six hospital subdistricts a similar distribution could be seen (*Figure 18*). All in all 43% of the patients in the centralised service model and 60% in the hybrid model never had the possibility of vascular surgical consultation prior to the first amputation (*Figure 18*).

Figure 18: CLI incidences in the different hospital subdistricts (age- and sex standardised incidences/100 000 aged 40 and over)



Assessment of the socio-economic features in the region showed the highest percentage of academic education, the highest tax income/inhabitant and the smallest invalidity pension incidence due to vascular diseases in the particular hospital subdistrict (Jorvi hospital) with the smallest CLI-incidence. In the subdistrict with the highest CLI-incidence (Lohja hospital) as well as the highest amputation incidence, the percentage of academic education as well as the tax income per inhabitant was among the lowest in the region whereas the disability pension incidence was among the highest. (*Table 17*).

Table 17: CLI incidences and socio-economic differences between health care areas



	mean tax income (FIM/inh)	% population with academic education/ trained professionals	invalidity pension due to vascular diseases/1000 inh
Hyvinkää	14200	25 / 34	3.88
Lohja	14337	21 / 34	4.52
Tammisaari	15034	21 / 30	4.78
Porvoo	15248	23 / 32	4.11
Peijas	17304	26 / 34	3.97
Jorvi	21871	39 / 30	2.79

10. DISCUSSION

10.1 Limitations of the study

Generally most clinical studies are not free from certain limiting factors and selection bias. This study was conducted in a normal clinical environment under typical limitations. No ideal conditions were present and some patient selection inevitably has occurred. An account on the limitations of the different parts of the study is given below.

Study I: Reproducibility of ABI measurements.

In part A of the study, no standards, such as measurements performed by an experienced vascular technician, were available which may cause some bias and limits the scientific value of the material. Therefore the median of the measurements in each vessel had to be used as a standard and the difference from this median was calculated for each measurement.

Study II: Predictive value of pressure measurements

As this study is conducted on conservatively treated patients, an apparent patient selection is present. At the time of the study, however, no femoropedal bypasses or bypasses to the distal calf arteries were performed and a major proportion of the patients included in the study had distal lesions. They were consequently excluded from operative treatment due to technical reasons. Therefore the patient population can be estimated to represent the overall CLI patient population to a considerable extent.

As only the relationship between pressure values and amputation risk is assessed in this study, the selection may be considered unimportant.

Study III: The proportion of claudication prior to CLI

This study was conducted in the outpatient clinic of an academic referral centre, which may cause some selection bias. The proportion of patients without symptoms of claudication prior to developing critical leg ischaemia may not reflect the situation in the general population. Therefore the results of this study used as a basis for incidence calculations may have some bias. The study merely quantifies the phenomenon frequently seen by vascular surgeons in their daily practice.

Study IV: Outcome of unreconstructed CLI

The study material partly consists of the same patients as those included in study II – therefore the same problem with a selected patient material exists. Similar selection bias can be observed when comparing amputation and mortality rates in vascular surgical and conservative series (*see Tables 10a-c in Chapter 6.6.2*). It is considered unethical to randomise patients receiving reconstructive or conservative treatment in the era of reconstructive vascular surgery. Since most of the critically ischaemic patients are being revascularised today, the opportunities for carrying out a study assessing the natural outcome of critical leg ischaemia have become even fewer. Still, the drawbacks of historical series and the applicability of their results are well known, and this study is by no means free of such limitations.

Study V: Comparison of three vascular surgical service models. The regional incidence of critical leg ischaemia and major amputations – impact of service models, their implementation and socio-economic factors.

In this study the onset of CLI is set arbitrarily to the date of admission on the first hospital visit for the treatment of CLI. Still, slowly progressing symptoms of CLI may have been present up to a year before the date of admission.

The retrieval of data is based on different registries, which are apt to register only certain types of patients. Those, who have not received any operative care for CLI, or did not undergo an amputation but died before that, are therefore not included into the study. The number of these patients is estimated to be quite limited, due to the far-reaching Finnish social health care system, and will not have much impact on the evaluation of the different health care models for treating CLI.

This study is based on registries alone and can therefore only be as accurate as the original registries are. Registry-derived data has its own pitfalls regarding inclusion of all patients and validity of the data (Bergqvist 1998). The validity of the Finnvasc-registry has been evaluated using a random sample and has been found to have a mean agreement of 93% with the original hospital records (Kantonen 1997). The Hospital discharge register kept by the National Centre of Welfare and Health is a direct copy of the electronic hospital data, the accuracy of which has not been evaluated so far.

Another feature limiting the value of this study is the fact that no endovascular procedures were included into the study. Endovascular procedures were not recorded into the hospital discharge register during the time of the study and the hospitals were not able to provide any data on them either. Therefore no incidences on endovascular procedures could be calculated. To give an overall picture of the endovascular activity in the region, percutaneous transluminal angioplasties performed for critical leg ischaemia at the referral centre and other hospitals of the region were counted (*Table 18*).

Table 18: Infrainguinal endovascular procedures performed for critical leg ischaemia

Year	1991	1992	1993	1994	1995	1996	1997
RC*	15	27	24	32	28	29	33
other	2	9	12	11	9	4	3
total	17	36	36	43	37	33	36

*= referral centre

10.2 Discussion

With limitations already dealt with, the results of this study have in general provided some answers to actual clinical problems, and may contribute to decision making within the vascular service influencing organisational decision-making.

A number of guidelines on how to classify and diagnose CLI are available (Ad Hoc Committee on Reporting Standards 1986, European Consensus Document 1992, Rutherford 1997, TASC 2000). The identification of ischaemic legs is, however, far more complicated. Generally defined rules do not necessarily fit into everyday clinical practice. This is particularly true in critical leg ischaemia. Therefore this study investigated the problems involved in the detection and recognition of CLI. To be able to refer patients to vascular surgical assessment and treatment in time, the suspicion of ischaemic aetiology of rest pain or ulcers has to arise in primary health care at an early stage. The presence of preliminary symptoms can be helpful and the aim was to assess the occurrence of such symptoms. The threshold to suspect vascular involvement should be low and whenever suspicion arises, objective methods to determine the existence of haemodynamically significant impairment of the blood supply are needed. Ankle pressure measurements using a Doppler-probe are recognised as the basic method of measurement for vascular surgical patients as they are non-invasive, easy to perform and as no elaborate equipment is needed. They are recommended as a basic tool even for general practitioners (Jonason 2002) and most institutions have the equipment needed readily available. The purpose of this study was to assess the reproducibility of Doppler derived pressure measurements in critically ischaemic patients in particular. The key question was whether arbitrary measurers are able to provide reliable distal pressure data and whether the pressure data is able to predict amputation risk.

An additional aim of the study was to investigate the fate of critically ischaemic patients, once critical leg ischaemia is diagnosed, as well as the outcome of treatment in different clinical settings. To accomplish this, the outcome of patients not receiving reconstructive surgery was assessed and the population-based outcome of treatment in different regions was evaluated. Specific therapeutic approaches are well studied and not within the scope of this study.

Study I: Reproducibility of ABI measurements

The results clearly show that the current measurement policy in many smaller vascular surgical units in this country, with the occasional physician, surgeon or nurse being appointed to perform ankle-brachial-pressure indices, is inadequate to provide reliable high quality measurements. Similar results have been reported previously by Kaiser who used claudication patients and Ray who used an unselected patient population to determine the reliability of measurements performed by inexperienced measurers (Kaiser 1999, Ray 1994). Specialised vascular nurses/technicians should be educated to reach internationally agreed levels of measurement accuracy, stating a clear case for vascular laboratories (Lepäntalo 1997). Measurements performed by inexperienced personnel can be regarded as qualitative assessments and should only be used to get a rough idea of the vascular status.

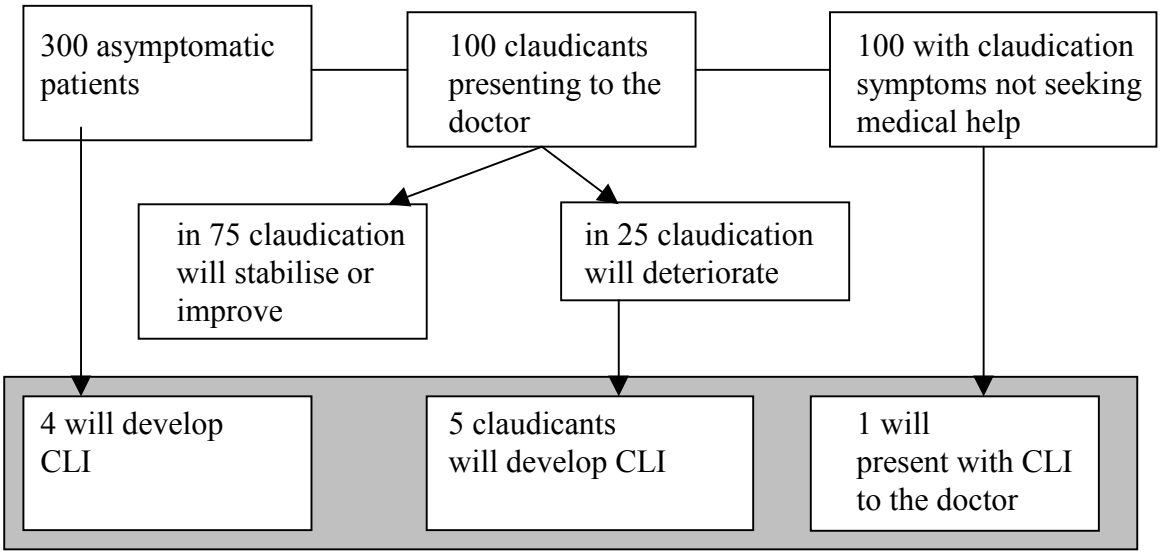
Study II: Predictive value of pressure measurements

Although pressure values have been seen to be associated with leg outcome (Vayssariat 1997), single pressure measurements proved to be inadequate for predicting the leg outcome in the present study. Likewise, it has been impossible to predict amputation stump healing with pressure measurements (Lepäntalo 1982, Lepäntalo 1987). Pressure measurements may give only supplementary information to clinical judgment (Lepäntalo 1988).

Study III: The proportion of claudication prior to CLI

The often used assumption in describing the course of PAD, that the symptoms of PAD progress slowly from asymptomatic, to claudication and finally to symptoms indicating critical ischaemia is incorrect according to the present study (*Figure 19*). Although the underlying PAD lesions may be severe enough to cause symptoms of claudication, there are various reasons causing the patient not to experience them. Therefore a significant proportion of the patients presenting to the doctor with symptoms of critical leg ischaemia, may not have experienced previous symptoms of claudication. Their complaints may be mistaken as caused by some other aetiology, thereby delaying the correct diagnosis and treatment.

Figure 19: The development of critical leg ischaemia
(Based on Figure 14 in the TASC document and modified according to the data of this study.)



The duration of symptoms indicating CLI as such seemed not to play a significant role in determining amputation risk, as in the subset analysis no correlation was found between the risk of amputation and the length of symptoms. This is a surprising finding, as international literature often stresses that it is essential to provide proper vascular treatment to critically ischaemic patients within 1-2 days (Audit Committee of the Vascular Surgical Society of Great Britain and Ireland 1996, TASC 2000), to avoid unnecessary deterioration of the condition of the leg due to treatment delay, which may possibly result in major amputations that could have been prevented if treated earlier.

One explanation of this finding may be that it is not possible to assess the nature and the progression of symptoms well enough by means of a simple questionnaire and interview. Etiological factors of the disease such as diabetes, presence of infection or neuropathy, concomitant diseases and activity differ. Furthermore the definition of CLI is only a recommendation that doesn't fully describe the clinical situation (TASC 2000). The definition of CLI contains ischaemia of varying severity. An elderly sedentary patient may have a slowly occluding vascular tree in the calf with an occasional small trauma and a wound, which does not heal. As long as this ulcer remains dry and non-infected, and it is not extensively debrided, the progression of the ulcer may be very slow. It may take months until the patient shows the ulcer to a physician. It may even take considerable time for the patient to realise the existence of an ulcer, if it does not cause any pain. This is a quite common phenomenon in diabetic patients with diabetic neuropathy. The opposite example would be a patient who may have had a similar trauma as above but whose wound subsequently becomes infected, causing severe pain and becoming larger within days. Such a patient is likely to seek medical help without delay and is likely to be referred to specialist care. Likewise the outcome of an ulcer classified according to the Armstrong classification, as 2c may be different to an ulcer classified as 3d (Armstrong 1998).

According to the results of this subset analysis it may be assumed that the present health care systems seem to be able to recognise the patients with a more fulminant course of the disease, sending them to receive vascular assessment and treatment in due course.

Study IV: Outcome of unreconstructed CLI

The annual amputation rate of critically ischaemic patients in the classic study of Bloor ranged between 23-57% with an increasing amputation rate at increasing age (Bloor 1961). When comparing these results to our series, with conservatively treated CLI patients followed up for 1 year before the era of femoropedal bypass surgery, the limb salvage rates were in accordance with Bloor's results (Lepäntalo 1996). Our one-year limb salvage was 54% in a patient group aged 40-96 with a mean age of 75 years. In Bloor's material 4% of the original claudicants were diabetics, but no report on the proportion of diabetics in the patient group developing CLI was available. In our material the proportion of diabetic patients was, however, much higher (50%). This probably mirrors the improvement of diabetes care leading to an increased life expectancy of diabetics and thereby developing an increasing number of vascular complications (Eskelinen 2004). The fact that in our study these patients constitute a patient group deemed unreconstructible, in conjunction with the high proportion of diabetics might worsen the outcome results. Because the study was conducted before the era of femoropedal bypass surgery, some of these patients would possibly have been evaluated operable today.

More recent series dealing with unreconstructed critical leg ischaemia have produced amputation rates ranging between 32 and 50% at 6 months of follow-up (Klomp 1999, Norgren 1990, UK Severe Limb Ischaemia Study Group 1991). These are similar to the rates achieved at one year in our study, indicating that in these studies the influence of patient selection may play an even greater role than in our study.

Mortality in patients with severe impairment of peripheral blood flow is high, due to the extent of the vascular disease and the large number of comorbidities frequently seen in this patient group. In unreconstructable patients mortality rates between 5 and 23% at six months have been reported (Belch 1983, Norgren 1990, UK Severe Limb Ischaemia Study Group 1991, Klomp 1999). In surgical series on critical leg ischaemia mortality rates between 15 and 30 % have been reported at one year (Wolfe 1986, Taylor 1991, Luther 1996b, Luther 1997a, Luther 1997c), which are much smaller than the mortality rate in our own study, where cumulative survival at one year was only 46%. This emphasises the difference in the patient materials and the fact that in our study some of the patients were excluded from surgical treatment due to high operative risk, which is bound to increase mortality.

As both the amputation risk and the mortality are high in critically ischaemic patients, the proportion to survive with a viable limb will be relatively small. In the present study the proportion of CLI-patients being alive with a preserved leg was only 28% at one year. In comparison, in an Iloprost study from the UK, 42% of the conservatively treated patients were alive with an intact leg at 6 months (UK Severe Limb Ischaemia Study Group 1991), while in an epidural stimulation study by Klomp et al 57% survived with an intact leg at 6 months. At 2 years the proportion retaining the leg and surviving was 34% (Klomp 1999). Although being better than the figures of the present study, these percentages illustrate the bleak prospect of critically ischaemic patients.

Study V: Comparison of vascular surgical service models

Each country, and often even each health care region, has its own solution for organising its health care. In order to modify the system according to the changing needs of the population (as well as dwindling financial resources), different systems should be subjected to scrutiny and evaluation. As resources are limited, each municipality seeks for the most effective and convenient way to provide its population with sufficient health care. Finland runs a very decentralised health care system, as every municipality does arrange their health care service the way it sees fit. Therefore the health care models can be different even within the catchment area of one single university hospital.

The success in preventing or delaying major amputations in patients with CLI seems to be tied to an aggressive policy of performing bypass procedures to crural and pedal vessels (Luther 2000, Eickhoff 1993, Eskelinen 2003), which require specialist skills and are provided in vascular centres. As failure to provide adequate vascular services for critically ischaemic patients inevitably results in increased amputation rates, the effectiveness of different service strategies could, at least in theory, be easily compared. It has been shown that patients undergoing an amputation utilise twice as much health care resources than those subjected to reconstructive procedures for CLI (Luther 1997c).

During the time period chosen for the present study the Finnvasc register provided fairly reliable data, having been evaluated for the first 4 years of this period (Kantonen 1997, Paaske in press). Later on the commitment to participate in the collection of data subsided in several centres. The Finnvasc data was complete up to the year 1996, but already in 1997 the data of one centre in Uusimaa was deficient and had to be retrieved from hospital records. In 1998 the data was even more incomplete and therefore the years 1991-1997 were selected for the study. Many hospitals have since founded own registries, which are not compatible with each other and do not cover the whole country. Data on all hospital stays of all patients is still recorded in the national discharge register, but as the ICD 10-coding, which is currently in use, does not differentiate between claudication and critical leg ischaemia, this data will not be of assistance, when assessing the fate of critically ischaemic patients.

In the present study major amputation rates were used as population-based age- and sex-adjusted incidences as a measure of the effectiveness of vascular surgical services in treatment of CLI (Luther 1996a). No clear difference in amputation rates between the three health care models could be detected, although the centralised model showed an association to lower amputation incidences in the regression analysis. The variation from year to year was considerable and so was the variation between the hospitals within the same health care model, even though the incidences were age- and sex standardised. This might be due to too small population samples. Similarly, the large differences between hospitals within the same referral model may also reflect the confounding influence of population differences, provision of vascular consultations and treatment delay.

The key observation of the study was, however, that the vascular referral strategies were not implemented properly. The hospitals preferred to maintain a fair amount of independence in their decision-making and decisions to amputate were made without vascular consultation. At that time Finland did not have vascular surgery as a speciality in its own right – the speciality was first established in 2000. Many patients were never seen by a vascular surgeon but were amputated primarily. Thus it is understandable that the active treatment policy of the academic referral centre did not seem to show any results on population basis. The present data emphasise the importance of an active implementation of referral strategies and an active treatment policy on every level of the treatment chain in order to achieve an improvement in amputation incidences (Lepäntalo 2000). Heikkinen et al (Heikkinen 2000) have shown that amputation rates are lowest in those municipalities that use vascular surgical services the

most. Furthermore, in a small region of some 170 000 inhabitants a well-organised vascular service has produced a magnificent decrease in amputation rates in association with increased vascular surgical activity (Luther 2002).

The influence of socio-economic factors has been shown for cardiovascular diseases (Salomaa 2001, Jousilahti 1998, Morrison 1997) and a similar association may be assumed to exist for peripheral vascular disease. In an attempt to explain the great differences in CLI-incidences in hospital subdistricts within the same referral model, a few socio-economic features of the municipalities in the study area were assessed. Some interaction between socio-economic factors and CLI-incidence was seen, which indicates that amputation rates do not only depend on the modality and efficiency of vascular surgical services, but on socio-economic factors as well.

Proper implementation of vascular referral and service strategies is necessary to decrease the amputation rates further, guaranteeing equal treatment to all patients and further enabling socio-economic- and cost-effectiveness studies in future.

In this study the actual costs of CLI treatment on population basis were intended for calculation. The calculations were to be based on the number of days spent in hospital, costs of the actual procedure, visits at the outpatient clinic, costs of the radiological and endovascular procedures as well as the days spent in intensive care. Additionally, the costs of the days spent in rehabilitation and nursing homes were to be calculated. The costs having occurred in the different vascular service models were to be compared with each other.

Only one hospital was able to provide all the information necessary for the calculations. Most of the other hospitals were not able to provide data on either the days spent in intensive care units, the outpatient clinic visits or the procedures performed in the radiology department. Additionally the task of determining the costs for each item proved to be impossible. At the beginning of the period all hospitals were charging their costs according to the days spent in hospitals without differentiating between intensive care, operative treatment or any other items. In one of the hospitals this was changed to calculating all items separate for a short time period (3 years) before joining the DRG-pricing (Diagnosis Related Groups). All other hospitals switched from the overall ward price to the DRG-system so that they were unable to determine separate prices for the items needed. It was also impossible to determine in retrospect which in-patient period belonged to which DR-Group, using the information provided from the hospital discharge register. However, the information on the costs actually charged to the patients' home municipality for each hospital visit was stored in a central coordinating and development centre of the hospital administration. The database had been designed for administrative purposes. Unfortunately part of the information on earlier years had been erased and backup tapes wiped, so that only information on the last year of the study period was available. In essence, the calculation of any relevant costs – especially the long-term costs – had been made impossible.

11. CONCLUSIONS

Critical leg ischaemia is comparable to a ”malignant” disease causing considerable morbidity. It is typically a disease of the elderly, but some risk factors such as diabetes can cause it to occur even in the middle-aged population. Tissue loss in ulcers and gangrene can be regarded to represent a similar condition in the foot, as myocardial infarction is for the heart, while rest pain is similar to unstable angina pectoris with the impending danger of losing some of the still viable tissue. It is indeed a manifestation of the same disease, as impairment of the arterial blood supply in the leg reflects the situation of the whole arterial tree. Therefore, patients with critical leg ischaemia often have several co-morbidities and the mortality is very high.

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14. ORIGINAL PUBLICATIONS

15. APPENDIX

Questionnaire for patients attending to the vascular outpatient clinic or the ward:
NAME_____ID_____
Date_____
Questions to be asked:
History and risk factors

Smoking ☐ yes ☐ no duration _____ amount_____ has quit _____ ago

Does the patient have at present /Did the patient use to have?: *Y=yes, N=no*
Diabetes Y N duration_____ insulin dependent diabetes Y N

Hypertension Y N duration_____ Hyperlipidaemia Y N

Chest pain/dyspnea during exercise Y N Myocardial infarction Y N CABG Y N

Renal disease Y N Serum-Kreatinine_____ Pulmonary disease Y N
☐ Renal transplantation ☐ Dialysis

Previous vascular surgery Y N Brain infarction/TIA Y N
What procedure _____

When did the patient first turn to a doctor due the present complaint in the legs?
_____ Where /To whom?_____

Symptoms
Does the patient have....?
claudication ☐ Yes ☐ No
if yes: for how long? _____

Location?

☐ right	☐ left
☐ foot	☐ foot
☐ calf	☐ calf
☐ thigh	☐ thigh
☐ buttock	☐ buttock
☐ other, specify _____	☐ other, specify _____

Nature of the symptoms? ☐ pain ☐ numbness etc.

When do the symptoms occur?
☐ at home ☐ outsideof the thouse ☐ walking uphill ☐ other , specify_____

Do the symptoms disappear after rest? ☐ Yes, how soon_____ ☐ No

Does the pain ever disappear while walking? ☐ Yes ☐ No

Does the patient have to stop walking because of some other complaint?
☐ Yes, which complaint_____ ☐ No

Did the patient previously experience claudication pain, that has subsequently subsided?

☐ **Yes, Location** _____ ☐ **No**

Rest pain ☐ Yes ☐ No
if yes: Duration _____

Location

☐ right	☐ left
☐ toe	☐ toe
☐ foot	☐ foot
☐ ankle	☐ ankle
☐ calf	☐ calf
☐ other, specify _____	☐ other, specify _____

Does the patient need regular pain killers for the rest pain? Yes ☐ No ☐

Ulcers ☐ Yes ☐ No
if yes: Duration _____

Location

☐ right	☐ left
☐ toe	☐ toe
☐ foot	☐ foot
☐ ankle	☐ ankle
☐ calf	☐ calf
☐ other, specify _____	☐ other, specify _____

Did the patient have previous ulcers that have healed after therapy? ☐ Yes ☐ No

Location? _____

Gangrene ☐ Yes ☐ No
if yes: Duration _____

Location

☐ right	☐ left
☐ toe	☐ toe
☐ foot	☐ foot
☐ ankle	☐ ankle
☐ calf	☐ calf
☐ other, specify _____	☐ other, specify _____

Vascular lab: date:__ __ __ __ __ __

Pressures	DX	SIN
ankle TP	_____	_____
ankle DP	_____	_____
toe	_____	_____
A.brachialis	_____	_____
ABI (ATP)	_____	_____
ABI (ADP)	_____	_____

other notes: