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Risk Factors, Survival and Impact of Invasive Treatment in Symptomatic Chronic Lower Limb Ischemia

ACADEMIC DISSERTATION
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ABBREVIATIONS

AAA	abdominal aortic aneurysm
ABI	ankle-brachial index
AFS	amputation-free survival
AK	above the knee
ASA	The American Society of Anesthesiologists classification
BASIL	Bypass versus Angioplasty in Severe Ischaemia of the Leg
BK	below the knee
CAD	coronary disease
CLI	critical limb ischaemia
CPM	Customised Probability Model
CRP	C-reactive protein
CTA	computed tomography angiography
DD	colour-assisted duplex ultrasonography
DM	diabetes mellitus
DSA	digital subtraction angiography
ECG	electrocardiogram
GAS	Glasgow aneurysm score
GetABI	German Epidemiological Trial on Ankle Brachial Index
IC	intermittent claudication
ICQ	Intermittent Claudication Questionnaire
LDL	low-density lipoprotein
MRA	magnetic resonance angiography
MOF	multi-organ failure

NHP	Nottingham Health Profile
PAD	peripheral arterial disease
POSSUM	Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity
PTA	percutaneous transluminal angioplasty
QoL	quality of life
SF-36	Short-Form 36 Health Survey
SPSS	Statistical Package for Social Sciences
TASC	TransAtlantic Inter-Society Consensus
TIA	transient ischemic attack
TP	toe pressure
VASCUQOL	Vascular Quality of Life Questionnaire

LIST OF ORIGINAL COMMUNICATIONS

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II Virkkunen J, Heikkinen M, Lepäntalo M, Metsänoja R, Salenius J. Diabetes as an independent risk factor for early postoperative complications in critical limb ischemia. Journal of Vascular Surgery 2004; 40: 761-767.

III Virkkunen J, Venermo M, Saarinen J, Keski-Nisula L, Apuli P, Kankainen A-L, Salenius J. Impact of endovascular treatment on clinical status and health-related quality of life. Scandinavian Journal of Surgery 2008; 97: 50-55.

IV Virkkunen J, Venermo M, Saarinen J, Salenius J. Predictors for the immediate and long-term outcome of a vascular surgical procedure. Scandinavian Journal of Surgery 2009; 98: 164-168.

ABSTRACT

Peripheral arterial disease (PAD) and its symptomatic form, chronic lower limb ischemia, present a growing challenge for the health care system in the western world due to the aging of the population. There is an increasing need to weigh the risks of the invasive treatments for PAD against the possible benefits of the same in terms of patient survival and quality of life. In addition to the anatomic locations of PAD lesions that determine what kind of treatment can be used, there are several quite well-known risk factors affecting the decision-making process.

The aim of the present study was to investigate the anatomical distribution of PAD lesions and the role of diabetes as a risk factor for surgery on critical limb ischemia, in addition to studying a possible model for identifying high-risk patients for surgery as well as examining the impact of endovascular treatment for chronic lower limb ischemia on the quality of life.

For the analysis of the anatomical locations of PAD lesions, 98 consecutive patients' (38 diabetics and 60 non-diabetics) digital subtraction angiographies were evaluated. The risk factors and outcomes after vascular surgical procedures were evaluated in two studies – the first was based on the retrospective Finnvasc national registry's 5,709 surgery patients operated for critical limb ischemia, and the second was a prospective clinical study on 157 consecutive patients undergoing vascular surgery. The impact of PTA (percutaneus transluminal angioplasty) treatment of chronic lower limb ischemia on clinical outcome and quality of life was investigated in a prospective clinical study including 61 consecutive patients undergoing PTA and suffering from claudication or critical limb ischemia.

As a result for the locations of PAD lesions, diabetics had less stenosis in the superficial femoral artery, but they had a tendency towards more diffuse atherosclerotic disease in their crural arteries.

In the multivariate analysis of the Finnvasc registry patients regarding the risks of surgery, diabetes was not an independent risk factor for early postoperative mortality in CLI, but morbidity was increased among diabetics in association with definitive risk factors. In a further study of risk factors and outcome after vascular surgery, the Glasgow Aneurysm Score (GAS) proved to have a good predictive value for outcome after vascular surgery among low-risk patients (GAS<77), but due to its low predictive value for death, GAS yields limited value in clinical practice. In the study on 61 PTA-treated patients, the impact of the treatment on the quality of life was examined using the Finnish version of the Nottingham health profile. For the claudicants, treatment resulted in an immediate improvement in the quality of life, but this effect seemed to vanish in the long term. However, there is a subgroup of CLI patients, for whom PTA led to significant benefits in terms of both limb salvage and quality of life.

1 INTRODUCTION AND REVIEW OF THE LITERATURE

1.1 Peripheral arterial disease

1.1.1 Introduction

Peripheral arterial disease (PAD) is a progressive atherosclerotic disease resulting in arterial stenosis and occlusions in non-coronary or non-carotid arteries. PAD is most often asymptomatic, and the most common clinical manifestation, due to its typical manifestation in at least one major vessel supplying the lower extremities, is chronic lower limb ischemia, intermittent claudication (IC), or critical limb ischemia (CLI). Sometimes the first clinical symptom is acute ischemia.

The total prevalence of asymptomatic PAD, as based on objective testing, has been evaluated in several epidemiologic studies and is in the range of 3%–10%, increasing to 15%–20% in persons aged over 70 years (Criqui et al., 1985, Hiatt, Hoag and Hamman, 1995, Selvin and Erlinger, 2004, Sigvant et al., 2007). Because the majority of patients are asymptomatic, the prevalence of PAD in the leg can only be estimated by using objective measurements in a general population. The ankle-brachial index (ABI) is a reliable non-invasive means to diagnose PAD. A resting value of ≤ 0.9 is most often used in epidemiological studies as a threshold value for the presence of PAD, with 80%–90% sensitivity and 95%–100% specificity (Guo et al., 2008, Norgren et al., 2007).

Although PAD is relatively common among the elderly population, the prevalence of symptomatic PAD is much lower (Diehm et al., 2004a). On the other hand, typical claudication symptoms may not occur in patients who have co-morbidities that prevent sufficient activity to produce limb symptoms or in patients who are too sedentary to walk (Norgren et al., 2007).

1.1.2 Claudication

IC is considered the most classic manifestation of PAD. IC usually refers to cramping pain in the musculature of the legs during exercise, and the pain is relieved within 10 minutes' rest from exercise (Norgren et al., 2007, Laing and Greenhalgh, 1980a). The pain is caused by an occlusive or stenotic lesion in the arterial supply of the leg muscles that interferes with the blood flow, producing ischemic pain with exercise. The localisation of the symptoms depends on the level of stenosis or occlusion in the arterial tree. Patients with an isolated occlusion of an internal iliac artery may have claudication in the buttocks, and impotence may occur in males. Occlusion or stenos of the common or external iliac artery may cause symptoms in the thigh and occlusion or stenosis of the femoral arteries in the calf. (Norgren et al., 2007). Based on several large population studies, the prevalence of IC is estimated to increase from roughly 3% in patients aged 40 to 6% in patents aged 60 years (Norgren et al., 2007)(Reunanen, Takkunen and Aromaa, 1982)(Hughson, Mann and Garrod, 1978)(Hirsch et al., 2001).

Although PAD is progressive in the pathological sense, the clinical course of claudication is stable in most cases, and approximately one quarter of patients with IC will deteriorate significantly (Norgren et al., 2007). From these 25%, only roughly 5%–10% will progress to critical limb ischemia over a 5-year period (Hirsch et al., 2006) .

1.1.3 Critical limb ischemia

The term CLI refers to a severe clinical manifestation of PAD, such as chronic ischemic rest pain and/or ischemic skin lesions, either ulcers or gangrene, with symptoms that have been present for more than 2 weeks with objectively proven arterial disease (Norgren et al., 2007). The reduction of blood supply threatens the leg, and without revascularisation, approximately 40% of the patients will have to undergo a major amputation and 20% will die within six months (Norgren et al., 2007, Rutherford et al., 1997a). Fontaine's stages and Rutherford's categories are widely used for the classification of PAD (Table 1). No absolute level of ABI or toe pressure (TP) can be set to indicate critical limb ischemia, but as a rough reference point, rest pain starts when ABI is below 40 mmHg or TP below 30 mmHg (Rutherford et al., 1997a). When a tissue lesion is present, higher pressure values have been proposed to fulfil CLI criteria, with ABI < 60 mmHg and TP < 40 mmHg (Rutherford et al., 1997a). The exact incidence of CLI is unknown. Patients will undergo a variety of medical treatments before their PAD has reached the stage of CLI. There is indirect evidence from studies looking at the progression of IC, in addition to population surveys on prevalence and assumptions based on amputation rates. Based on these studies, there are approximately 500–1,000 / million new cases of CLI every year in the European or North American population. (Dormandy, Heeck and Vig, 1999)(Norgren et al., 2007).

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

Table 1. Classification of peripheral arterial disease: Fontaine's stages and Rutherford's categories. (Modified from: TASC working group 2007).

1.2 Risk factors for PAD

PAD is highly associated with traditional cardiovascular disease risk factors. It is essential to understand that in most cases the progression of PAD is the sum of various risk factors rather than a consequence a certain risk factor (Figure 1). It is also important to identify these risk factors, because influencing them lowers the total cardiovascular risk in PAD patients, and the progression of PAD may also decrease (Hirsch et al., 2006). Patients with PAD have a high overall risk of death from cardiovascular causes (Criqui et al., 1992).

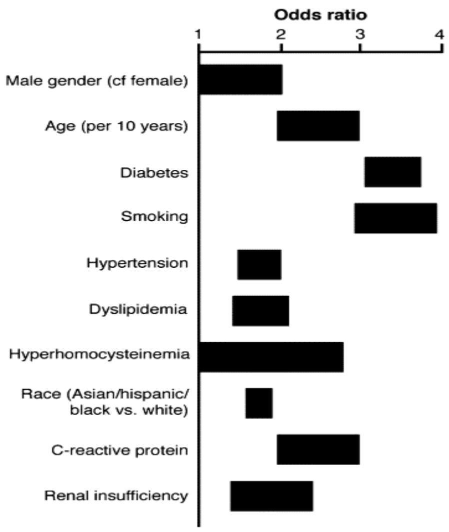


Figure 1. Approximate range of odds ratios for the risk factors of symptomatic peripheral arterial disease. (Modified from TASC working group 2007.)

1.2.1 Smoking

Current smoking is highly associated with PAD, and this relation was first recognised in 1911 by Erb, when the risk of IC was reported to be three times greater in smokers (Erb, 1911). In the Framingham study, the risk of PAD was documented to be twice as high in smokers when compared with non-smokers (Kannel, Castelli and McNamara, 1968). This finding has been confirmed by several other epidemiological studies, the relative risk ratios ranging from 1.7 to 7.5 (Reunanen, Takkunen and Aromaa, 1982, Hughson, Mann and Garrod, 1978, Schroll and Munck, 1981, Gofin et al., 1987). In a recent study, He et al. (He et al., 2008) also showed a positive association between passive smoking and the prevalence of PAD.

1.2.2 Diabetes

Diabetes is highly associated with PAD, and a low ABI is highly prevalent in subjects with diabetes (Gordon and Kannel, 1972)(Mostaza et al., 2008). Diabetes increases the risk of PAD approximately three- to four-fold and the risk of IC two-fold (Norgren et al., 2007). Furthermore, in diabetic patients, the limb-salvage rate in CLI has been reported to be lower and the major amputation rate higher than in non-diabetic PAD patients (Gottsater, 2006). Insulin resistance has been established as a risk factor for PAD even in patients without diabetes, raising the risk by approximately 40%–50% (Muntner et al., 2005).

The number of diabetics is increasing, and recent estimates suggest that 195 million people worldwide suffer from diabetes: This number will increase to 330 or perhaps to as high as 500 million by 2030 (King, Aubert and Herman, 1998, Engelgau et al., 2004). Furthermore, several epidemiological studies estimate that up to 50% of all patients with type 2 diabetes are undiagnosed

(Borch-Johnsen et al., 1998)(Harris et al., 1998)(Rathmann et al., 2003), since they remain asymptomatic for many years.

The nature of PAD is often more subtle in its presentation in diabetics, although the association with diabetes is well known. PAD in individuals with diabetes is usually accompanied by peripheral neuropathy with impaired sensory feedback. Therefore, a classic history of claudication may be less common and the patient may elicit more subtle symptoms, such as leg fatigue and slow walking velocity, and simply attribute this to getting older (American Diabetes Association, 2003). It has been reported that patients with diabetes and PAD experience worse lower-extremity function than those with PAD alone (Dolan et al., 2002) who suffer from claudication. For these reasons, a patient with diabetes and PAD may be more likely to present with an ischemic ulcer or gangrene than a patient without diabetes.

Early diagnosis of PAD is extremely important in diabetic patients with regard to preventing the progression of peripheral vascular disease. The vascular obstructions or stenosis in diabetics are often located more distally than in non-diabetics, being typically in the popliteal artery or in the crural arteries (Jude et al., 2001)(Strandness, Priest and Gibbons, 1964). The calcification of the media layer of the arteries is also a typical phenomenon of diabetic PAD (Everhart et al., 1988), which may cause a falsely high ABI index as a result of stiff arterial walls. On the other hand, it is important to consider that ulcers may often exist in a diabetic foot despite normal macrocirculation. These ulcers usually occur due to neuropathy, including disturbances in the microcirculation, as well as trauma and infection. (Boulton, 2008)(Jeffcoate et al., 2008).(Oyibo et al., 2001) Because the treatment of neuropathic ulcers is mainly non-surgical, the initial assessment must differentiate patients with a predominantly ischemic versus neuropathic cause. The provider must also establish the extent of any neuropathy or vascular disease (Adam, Raptis and Fitridge, 2006), which includes testing for sensation, palpating for foot pulses, measuring the ABI and toe pressures, and often undertaking colour-flow duplex ultrasonography (Adam, Raptis and Fitridge, 2006, Cavanagh et al., 2005).

1.2.3 Age

The prevalence of PAD increases with age, and in the highest age groups of 65–85 years, 20%–50% of the population are believed to have PAD, depending on the study design (Diehm et al., 2004a, Hirsch et al., 2001, Suominen et al., 2008a, Heidrich, Wenk and Hesse, 2004, Meijer et al., 1998). The prevalence of PAD peaks at the age of approximately 85 and decreases in nonagenarians to the level of 22%, being mostly asymptomatic (Suominen et al., 2008a).

1.2.4 Dyslipidemia

Hyperlipidemia is a well-established risk factor for PAD (Murabito et al., 1997) (Newman et al., 1993), and accumulating evidence provides that treatment of hyperlipidemia reduces the progression of atherosclerosis in the peripheral arteries (Duffield et al., 1983)(Newman et al., 1993). According to the European guidelines of cardiovascular disease prevention in clinical practise (De Backer et al., 2003), total plasma cholesterol should be below 5.0 mmol/l and low-density lipoprotein cholesterol (LDL) below 3.0 mmol/l. For patients with established cardiovascular disease or diabetes, the threshold values are stricter: total cholesterol < 4.5 mmol/l and LDL < 2.5 mmol/l (De Backer et al., 2003). In a recent study (Daskalopoulou et al., 2008), ABI correlated inversely with LDL levels in patients with newly diagnosed PAD who were not treated with lipid-lowering drugs. An association between PAD and hypertriglyceridemia has also been reported and shown to be associated with the progression and systemic complications of PAD (Norgren et al., 2007).

1.2.5 Sex

The prevalence of PAD in the general population is slightly greater in men than women, particularly in the younger age groups (Norgren et al., 2007). Selvin et al. did not find clear sex-related differences in PAD prevalence in their study with 2,174 participants aged 40 years and older from the 1999–2000 National Health and Nutritional Survey (Selvin and Erlinger, 2004). In a recent large population-based study of PAD, Sigvant et al. revealed a new observation that women dominate among those with PAD when the definition is based only on ABI (Sigvant et al., 2007). In the GetABI study, the prevalence of both symptomatic and asymptomatic PAD was higher among men than women, but in an analysis of subjects over 85 years of age, the prevalence of both symptomatic and asymptomatic PAD was higher among women (Diehm et al., 2004b). Other studies have shown that women with PAD had a higher prevalence of leg pain on exertion and rest as well as poorer functioning and greater walking impairment due to leg symptoms than men with PAD (McDermott et al., 2003). In conclusion, in a younger population the prevalence of PAD is higher among men, but in a population aged over 85 years, the prevalence is higher among women.

1.2.6 Renal insufficiency

Many studies have reported both cross-sectional and longitudinal associations between baseline renal insufficiency and PAD (O'Hare et al., 2005)(Daskalopoulou et al., 2008). Among end-stage renal disease patients, the prevalence of PAD appears to be much higher than in the general population (O'Hare and Johansen, 2002). In a study with IC patients, Daskalopoulou found a significant inverse correlation between ABI and serum creatinine level as well as estimated glomerular filtration rate (Daskalopoulou et al., 2008).

1.2.7 Other risk factors

Hypertension is a risk factor for cardiovascular diseases, both coronary heart disease (CHD) and cerebrovascular disease, as well as PAD (De Buyzere and Clement, 2008). The relative risk of developing PAD is lower in connection with hypertension as opposed to diabetes or smoking (Norgren et al., 2007), but hypertension and PAD combined cause a high total risk of cardiovascular events (De Buyzere and Clement, 2008)(De Buyzere and Clement, 2008) Several epidemiological surveys demonstrate a straightforward and independent relationship between increased blood pressure and the prevalence or incidence of PAD (De Buyzere and Clement, 2008). Especially systolic hypertension is characterised by the presence of PAD (Safar et al., 2008).

The prevalence of hyperhomocysteinemia is high (5%–10%)(Humphrey et al., 2008) in the vascular disease population, while it is only 1% in the general population (Norgren et al., 2007). The association between PAD and hyperhomocysteinemia is strong, increasing especially the risk associated with smoking and hypertension. A high serum homocysteine concentration may be an independent risk factor for PAD, as well as for cerebrovascular disease and CHD (Graham et al., 1997). A reduction of homocysteine levels has been accomplished by supplementation of the diet with vitamin B preparations (folate, vitamins B_6 and B_{12}), and in patients with hereditary homocystinuria, resulting in severe homocysteinemia (plasma concentrations >100 µmol/L), treatment with high-dose vitamin B in combination with dietary methionine restriction has resulted in a marked reduction of adverse vascular events (Yap et al., 2001). In contrast, results from trials aimed at lowering homocysteine levels in patients with mild hyperhomocysteinemia (10–30 μmol/L) have been disappointing, and the contradictory results have been attributed to trial design, with the potential adverse effects of vitamin B or homocysteine being rather a risk marker than a risk factor (Milani and Lavie, 2008)(Humphrey et al., 2008).

The prevalence of PAD has been reported to vary somewhat by ethnicity, although published comparisons mainly concern non-Hispanics Whites, blacks, Hispanics and Asians (Ix et al., 2008). The National Health and Nutritional Survey in the United States found that ABI $\leq$ 0.90 was more common in non-Hispanic Blacks than in Whites (Selvin and Erlinger, 2004). The reason for the excess prevalence of PAD among African-Americans was thought to be a higher rate of associated risk factors such as diabetes and hypertension. It was also speculated whether the risk factors of PAD in African-Americans might represent less aggressive treatment of said risk factors. In a recent study by Criqui (Criqui et al., 2005), black ethnicity seemed to be a strong and independent risk factor for PAD, and it was not explained by higher levels of other known risk factors (Criqui et al., 2005)(Ix et al., 2008).

Plasma C-reactive protein (CRP) is a marker of underlying systemic inflammation. It is produced by the liver in response to cytokines, which increases in the presence of atherosclerosis and cardiovascular risk factors (Libby and Ridker, 1999). An elevated CRP level has been considered to be a risk factor for PAD (Pradhan, Rifai and Ridker, 2002, Rohde et al., 1998). A recent study by Dascapopoulou demonstrated that the ABI was significantly inversely correlated with creatinine, CRP and fibrinogen levels (Daskalopoulou et al., 2008). Zacho showed in his study that polymorphisms in the CRP gene are associated with marked increases in CRP levels and thus with a theoretically predicted increase in the risk of ischemic vascular disease. However, these polymorphisms are not in themselves associated with an increased risk of ischemic vascular disease

(Zacho et al., 2008). The elevated CRP level is therefore rather the indicator for PAD than a risk factor for the development of PAD.

1.3 Diagnosis of PAD

A thorough anamnesis combined with physical examination is the cornerstone when evaluating a patient with suspected PAD. The physical examination should assess the circulatory system as a whole, and the specific peripheral vascular examination requires palpation of pulses from the inguinal, popliteal and ankle levels. In younger patients with no PAD risk factors, pulse palpation enables physicians to exclude the diagnosis of PAD with a high degree of certainty (Stoffers et al., 1997). On the other hand, despite the utility of the pulse examination, the finding of absent pedal pulses tends to over-diagnose PAD, whereas using the symptom of classic claudication to identify PAD will lead to a significant under-diagnosis (Schroll and Munck, 1981, Diehm et al., 2004b) (Norgren et al., 2007). Therefore, patients with a history or an examination suggestive of PAD, or when symptoms of CLI are suspected according to Fontaine's stages (Fontaine, Kim and Kieny, 1954) and Rutherford's categories (Rutherford et al., 1997b)(table 1), PAD must be confirmed with objective testing. Non-invasive methods to confirm the diagnosis of PAD include ABI measurement, segmental limb pressures, pulse volume recordings, toe pressure, transcutaneous oxygen tension test, and stress test.

1.3.1 Hemodynamic investigations

Measuring the pressure in the ankle arteries has become a standard part of the initial evaluation of patients with suspected PAD. A common method of measurement uses a manometer cuff placed just above the ankle, with a Doppler probe used to measure the systolic pressure of the posterior tibial and dorsalis pedis arteries of each leg (Figure 2). These pressures are then normalised to the higher brachial pressure of either arm to form the ABI, dividing the highest systolic blood pressure in the arteries at the ankle and foot by the higher of the two systolic blood pressures in the arms. An ABI ≤ 0.9 is typically considered diagnostic for PAD (Norgren et al., 2007), although the prevalence of PAD among people of an advanced age with elevated ABI (1.3–1.5) has lately been observed to be significantly probable especially among those with chronic renal failure, a history of smoking, CHD and severe lower extremity symptoms (Suominen et al., 2008b)

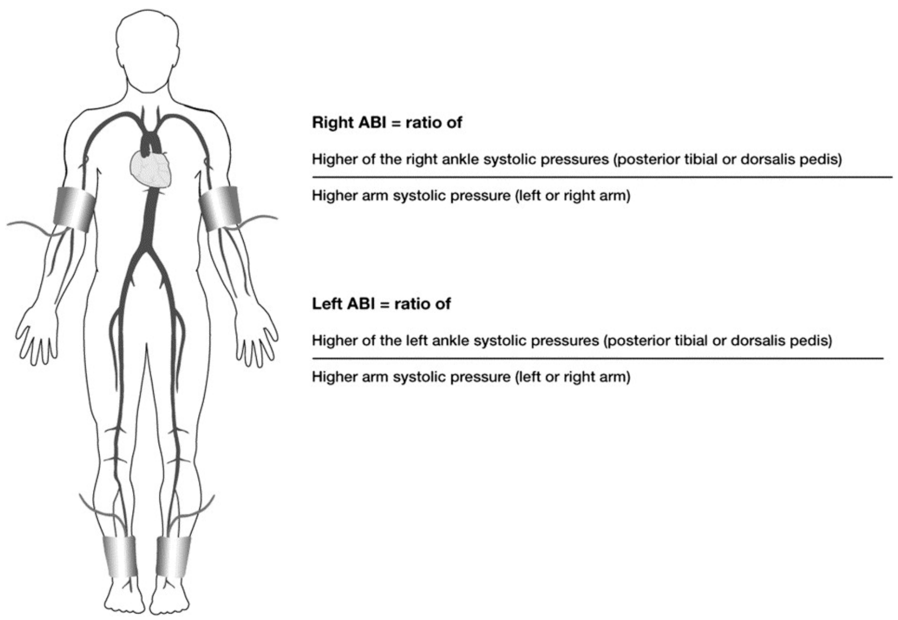


Figure 2. Measurement of the ankle-brachial index (ABI). (Modified from TASC working group 2007.)

1.3.2 Treadmill exercise test

A treadmill exercise test as a measure walking distance or walking time is subject to a variety of errors, including the effect of learning, other manifestations of atherosclerotic disease and limited physical performance capacity, and, in this regard, it has proven unreliable (Laing and Greenhalgh, 1980b, Perakyla et al., 1998). The maximum walking distance measured by a progressive exercise test exhibits better reproducibility than any other direct measure of walking distance (Perakyla et al., 1998). The treadmill test should be combined with other investigations, and the post-exercise-test ABI has proven useful in screening arterial insufficiency in the lower limb (Lepantalo, Lindfors and Pekkola, 1983) .

1.3.3 Imaging techniques

Imaging of the lower limb arteries is indicated whenever some kind of revascularisation procedure is indicated, if a suitable lesion is localised for either an endovascular or open surgical technique. The current options for imaging are digital subtraction angiography (DSA), colour-assisted duplex ultrasonography (DD), magnetic resonance angiography (MRA) and computed tomography angiography (CTA). The sensitivity and specificity of DD, MRA and CTA, using the DSA as a golden standard, is 80%–95% in arterial stenosis and 90% –99% in occlusions (Adriaensen et al., 2004)(AbuRahma, Khan and Robinson, 1995)(Hentsch et al., 2003)(Perreault et al., 2003)(Portugaller et al., 2003). Potential side effects and contraindications should be considered in choosing the imaging modality, in addition to allowing for local availability, experience and cost.

Angiography carries certain risks: an approximately 0.1% risk of severe reaction to contrast medium, a 0.7% risk severe enough to alter patient management, and a 0.16% mortality risk

(Norgren et al., 2007). Other complications include arterial dissection, atheroemboli, contrast medium-induced renal failure as well as access site complications including pseudoaneurysm formation, arteriovenous fistula and haematoma (Norgren et al., 2007). CTA is less invasive than angiography, but the major limitations of CTA include the usage of iodine contrast medium and radiation exposure (Jakobs, Wintersperger and Becker, 2004).

Colour-assisted ultrasonography is completely safe and much less expensive than the previously-mentioned angiography and CTA or MRA, providing most of the essential anatomic and hemodynamic information. The lower extremity arterial tree can be visualised, with the extent and degree of lesions accurately assessed and arterial velocities measured. Proper examination of the leg demands experience and skill, and crural arteries are challenging to image in their entirety. (Norgren et al., 2007) .

The advantages of MRA are safety and the ability to provide rapid high-resolution three-dimensional imaging of the entire arterial tree in one setting without arterial puncture. The high-field strength in MRA excludes patients with different variations of implants – for example, pace makers, spinal cord stimulators and intracerebral shunts – and the technique also excludes patients affected by claustrophobia that is not amenable to sedation. MRA is useful for treatment planning prior to intervention and in assessing the suitability of lesions for endovascular approaches, thus minimising the use of iodinated contrast medium and the exposure to radiation (Hentsch et al., 2003)(Norgren et al., 2007) .

1.4 Conservative treatment of PAD

1.4.1 Risk factor modification

Patients with PAD typically have multiple cardiovascular risk factors, and an essential element of conservative treatment of PAD is to influence the risk factors. Alongside the actual treatment of PAD, risk factor modification diminishes the overall risk of cardiovascular events. Smoking cessation alone slows the progression of PAD in CLI and reduces the risk of death due to vascular causes (Girolami et al., 1999). With regard to the treatment of hyperlipidemia, the target value for low-density lipoprotein cholesterol should be less than 2.5 mmol/l and for total serum cholesterol under 4.5 mmol/l (De Backer et al., 2003)(Tikkanen et al., 2004). Although it is unclear whether aggressive blood glucose lowering will protect peripheral circulation and prevent amputation (Norgren et al., 2007), the target for patients with DM (diabetes mellitus) is a haemoglobin A_{1C} level of less than 7.0%, and a level as close to 6.0% as possible should be targeted (Groop et al., 2007). Hypertension guidelines support the aggressive treatment of blood pressure in patients with PAD, and the current recommendation is a level of <140/90 mmHg and <130/80 if the patient also has DM or renal insufficiency (Bonny et al., 2008) (Jula et al., 2006).

1.4.2 Antiplatelet therapy

Aspirin is a well-recognised antiplatelet drug for secondary prevention that reduces the risk of adverse cardiovascular outcomes in patients with cardiovascular disease by approximately 25% (Antithrombotic Trialists' Collaboration, 2002). Current recommendations are to use antiplatelet therapy in all PAD patients with or without a history of other cardiovascular diseases (coronary or carotid arterial disease) to reduce the risk of cardiovascular morbidity and mortality, and the use of aspirin should be considered in patients with PAD exhibiting no clinical evidence of other forms of cardiovascular disease (Norgren et al., 2007). According to numerous publications from the Antithrombotic Trialists' Collaboration, low-dose aspirin (75–160 mg) is protective and probably safer in terms of gastrointestinal bleeding than higher doses of aspirin (Antithrombotic Trialists' Collaboration, 2002).

Clopidogrel has proven effective in reducing cardiovascular events in patients with PAD, with or without other clinical evidence of CHD (Norgren et al., 2007). The Clopidogrel Versus Aspirin in Patients at Risk if Ischaemic Events (CAPRIE) trial assessed the relative efficacy of Clopidogrel (75 mg/day) and aspirin (325/day) in reducing the risk of a composite outcome cluster of ischemic stroke, myocardial infarction or vascular death, and their relative safety was also assessed. The population studied comprised subgroups of 19,185 patients with atherosclerotic vascular disease manifested as either recent ischemic stroke, recent myocardial infarction or symptomatic PAD, and they were followed 1–3 years. There were 1,960 first events included in the outcome cluster, and patients treated with clopidogrel had an annual 5.32% risk of ischemic stroke, myocardial infarction or vascular death, as opposed to the 5.83% risk with aspirin. These rates reached a statistically significant ($p = 0.043$) relative risk reduction of 8.7% in favour of clopidogrel.(CAPRIE Steering Committee, 1996).

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial assessed the combination of aspirin (75–162 mg/day) and clopidogrel (75 mg/day), n = 7 802, and the combination of aspirin and placebo, n = 7 801, for the prevention of atherothrombotic events in high risk patients. As a result, the combination of clopidogrel and aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke or death from cardiovascular causes among patients with stabile cardiovascular disease or multiple cardiovascular risk factors. Furthermore, the risk of moderate to severe bleeding was increased. (Bhatt et al., 2006).

In a recommendation of the ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease, antiplatelet therapy is indicated to reduce the risk of myocardial infarction, stroke or death in individuals with PAD, and aspirin, in daily doses of 75–375 mg, is recommended as a safe and effective therapy. Clopidogrel (75 mg/day) is recommended as an effective alternative antiplatelet therapy to aspirin. (Hirsch et al., 2006). Oral anticoagulation therapy with warfarin is not indicated to reduce the risk of adverse cardiovascular ischemic events in individuals with PAD (Hirsch et al., 2006).

1.4.3 Non-invasive treatment of claudication

Patients with IC and PAD should all undergo the previously-mentioned risk factor modification treatment and antiplatelet therapy to reduce the risk of cardiovascular events. These activities, however, do not provide a significant reduction or elimination of the symptoms of IC. A number of medications have been developed for treating the symptoms of IC, with the phosphodiesterase type 3 inhibitor cilostazol and the methylxanthine derative pentoxifylline in clinical use. At any rate, the evidence of clinical utility remains quite unsatisfying because of poor effect or danger of major side effects (Norgren et al., 2007)(Ferreira and Macedo, 2010).

A supervised exercise programme for improving exercise performance and walking ability has been established by a considerable body of evidence to yield clinical benefits for the symptoms of IC (Gardner and Poehlman, 1995, Stewart et al., 2002)(Norgren et al., 2007). One meta-analysis (Gardner and Poehlman, 1995) that examined both randomised and non-randomised trials showed that exercise training improved pain-free walking time by an average of 180% and maximal walking time by an average of 120%. Exercise-induced improvement in walking ability has proven to improve coping with routine daily activities (Clifford et al., 1980), and such increases in activity in association with improvements in cardiovascular risk factors might also reduce the risk of adverse cardiovascular events (Regensteiner, Steiner and Hiatt, 1996). However, there are no data to support the efficacy of general and unstructured recommendations by the physician, which is still the most typical exercise prescription for patients with claudication (Norgren et al., 2007, Stewart et al., 2002).

1.5 Invasive treatment of PAD

If, despite exercise, smoking cessation and risk factor modification, the patient's quality of life is significantly reduced due to claudication, revascularisation procedures may be indicated, especially if the arterial lesion behind the symptoms is localised to the aortofemoral region. Three treatment methods are currently available: endovascular and surgical revascularisation or the combination of the same. The role of surgical bypass in claudication is poorly defined especially for infrainguinal disease. The morbidity and mortality associated with operating on a group of patients with a high prevalence of CHD, combined with the significant failure rate of bypass grafting, in a condition that has a relatively benign prognosis concerning the fate of the leg render this option very controversial. Single or multiple aortoiliacal stenosis totalling 10 cm and unilateral short (≤ 3 cm) occlusion is suggested for endovascular therapy (Norgren et al., 2007). For patients with disabling claudication and a low-risk profile, surgical revascularization may be considered in the case of severe aortofemoral lesions (Norgren et al., 2007).

The natural prognosis of CLI is such that intervention, endovascular or surgical, is indicated to salvage a useful and pain-free extremity. The treatment chosen always depends on the general condition of the patient and the extremity as well as an estimation of the risk of intervention based on co-morbid conditions and the expected patency and durability of reconstruction (Norgren et al., 2007)(Figure 3).

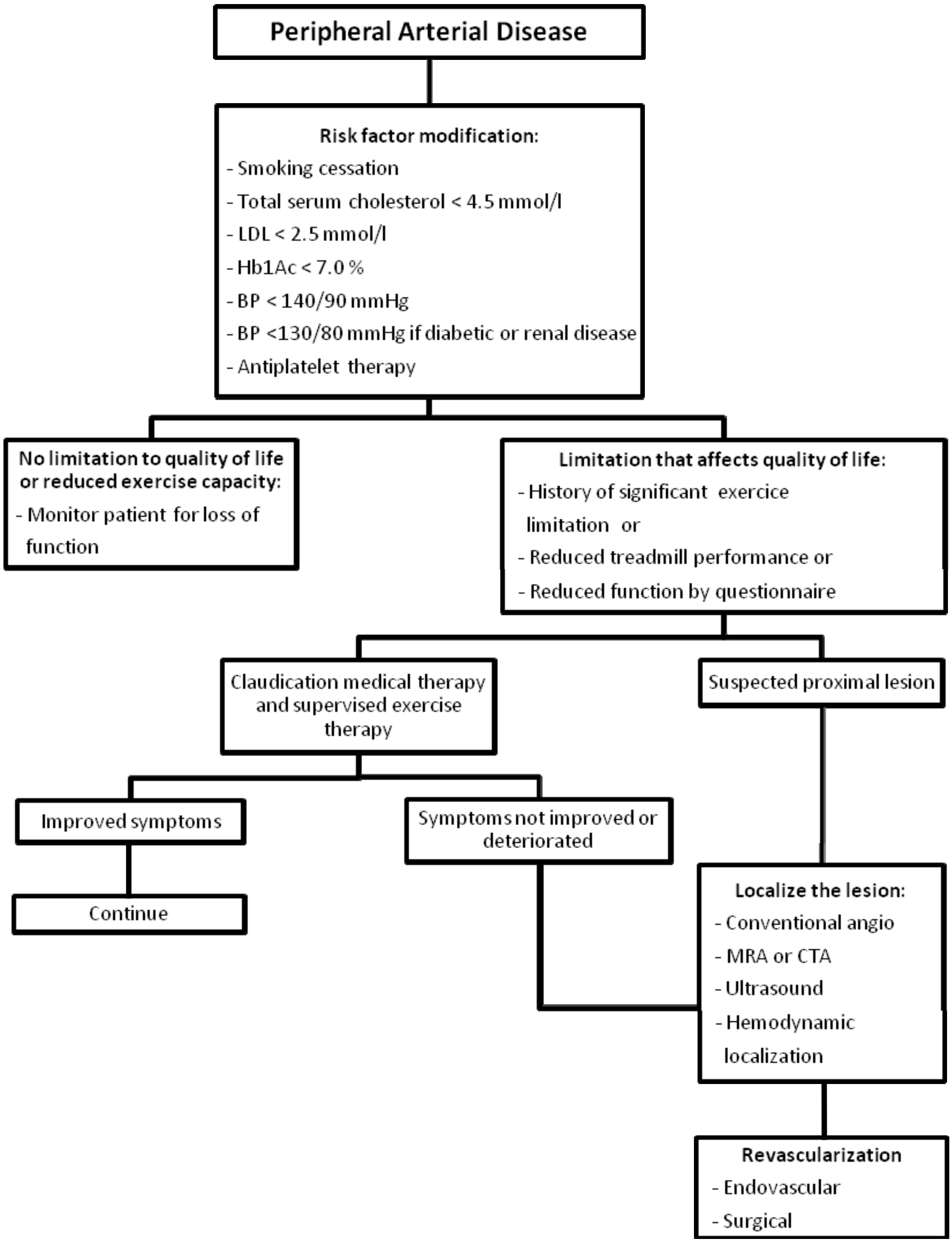


Figure 3. Overall treatment strategy for peripheral arterial disease. BP, blood pressure; HbA1c, hemoglobin A1c; LDL, low density lipoprotein; MRA, magnetic resonance angiography; CTA, computed tomographic angiography. (Modified from Hiatt WR. *N Engl J Med* 2001;344:1608 1621.)

In a study by Currie et al., successful endovascular treatment of claudication compared to unsupervised exercise results in a significant improvement in the patient's quality of life (QoL) in the domains of physical functioning ($p < 0.001$), physical role ($p < 0.005$), pain ($p < 0.001$) and vitality ($p < 0.05$) after 3 months' follow-up (Currie et al., 1995). However, to achieve this, the arterial lesion behind the symptoms must be suitable for endovascular treatment. In the study of Chetter et al., endovascular treatment resulted an immediate and lasting improvement in the QoL of claudicants, with unilateral claudicants with a solitary iliac lesion demonstrating the most marked QoL benefit during a 12-month follow-up (Chetter et al., 1998). However, infrapopliteal endovascular procedures are recommended only if patients have CLI, but not in claudication (Norgren et al., 2007). Endovascular techniques must be safe and focused on those likely to obtain long-term benefit, and they must be opted for after an attempt at non-invasive treatment.

The question whether endovascular or surgical revascularisation is the best method of the treatment of CLI is controversial. At present, there is only one multi-centre randomised controlled trial, the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) (Adam et al., 2005), comparing these two different treatments. The published results of the BASIL trial indicate that patients presenting with severe limb ischemia due to infrainguinal atherosclerosis who seem technically suitable for both treatments can reasonably be treated with either method. In the BASIL trial, the scope of generalisation of the study was audited. During the 6-month BASIL audit, 585 consecutive patients presented with severe limb ischemia and underwent diagnostic imaging. Of these, 129 (22%) needed supra-inguinal intervention and were not candidates for the trial. Of the remaining 456 patients, 220 (48%) were treated without revascularization and 236 (52%) underwent revascularization. Only 70 (30%) of the 236 patients with severe limb ischemia were regarded as suitable for randomisation into BASIL, and of these, 22 (31%) refused trial entry – the remaining 48 (69%) were randomised, being suitable for both treatment methods (Adam et al., 2005). The medium-term outcomes after angioplasty and surgery in BASIL were broadly similar with respect to amputation-free survival, all-cause mortality and health-related quality of life. In the short term, the surgically treated were associated with a significantly higher rate of morbidity, longer hospital stays and greater use of the high-dependency unit and intensive therapy unit than those treated with angioplasty. Therefore, hospital costs of surgery for the first 12 months were approximately one third higher than those of angioplasty. In the long term, after 2 years, surgery seemed to be associated with a significantly reduced risk of future amputation, improved durability and reduced re-intervention rate, which implicated that surgery could outweigh the short-term considerations of increased morbidity and cost.(Adam et al., 2005).

Based on BASIL, with due consideration to the poor generalizability of the trial, the high failure and re-intervention rate associated with angioplasty leads to the conclusion that patients who are expected to live less than 1–2 years and have significant co-morbidities should probably be offered angioplasty as a first-line treatment. By contrast, in patients expected to live more than 2 years who are relatively fit, the apparent improved durability and reduced re-intervention rate of bypass surgery seem to favour surgery (Adam et al., 2005).

1.6 Risk stratification in CLI

The prognosis of a patient with CLI is extremely poor. The natural history of patients with CLI is impossible to describe, because the majority of these patients receive some form of active treatment. Large surveys suggest that approximately half of CLI patients will undergo some type of revascularisation, roughly a quarter receive medical treatment only, and the rest will require a primary amputation. After one year, only some 25% of the patients are still alive with their leg and CLI resolved, and because of general atherosclerosis, the majority of the morbidity and mortality derives from cardiovascular reasons, including major limb loss, myocardial infarction, stroke and death (Lepantalo and Matzke, 1996)(Norgren et al., 2007)(Adam et al., 2005)(Figure 4). Therefore, in order to deem a revascularisation procedure a successful and worthwhile endeavour, there should be a reasonable probability that the patient will remain alive for one year with the treated limb (Second european consensus document on chronic critical leg ischemia. 1992). Otherwise, alternative therapies including conservative care or primary amputation should be strongly considered.

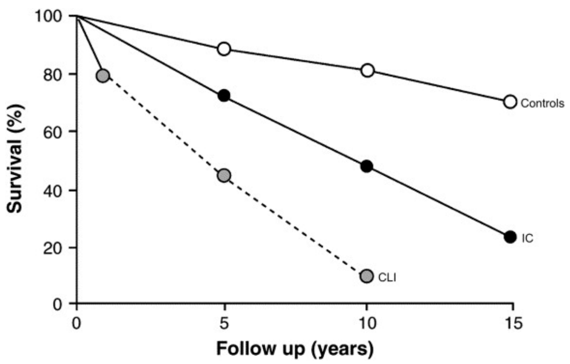


Figure 4. Survival of patients with peripheral arterial disease. IC, intermittent claudication; CLI, critical limb ischemia. (Modified from TASC working group 2007.)

1.6.1 Risk assessment of patients undergoing major non-cardiac surgery

The purpose of preoperative risk assessment of patients undergoing major surgery is to identify patients at increased risk for perioperative mortality and morbidity. Since perioperative cardiac mortality and morbidity are the most frequently occurring adverse events in major non-cardiac surgery and vascular surgery, most developed risk indexes (Lee index (Kertai et al., 2005), Eagle score(Eagle et al., 1989b), Vanzetto score (Vanzetto et al., 1996)(Kertai et al., 2005)) have focused on the evaluation of perioperative cardiac risk, and vascular surgery patients are well-identified as high cardiac risk patients (Eagle et al., 1996).

The American Society of Anesthesiologists classification (ASA) (1963) has received wide acceptance, but it is used to evaluate the physical status of the patient preoperatively and is not intended for use as a risk adjustment tool (Wolters et al., 2006). A good correlation between mortality and the ASA has been established (Hall and Hall, 1996)(Wolters et al., 1997), as well as a correlation with respect to morbidity (Wolters et al., 1997). In a prospective study on a group of PAD patients receiving an aorto-bi-iliac or aorto-bifemoral bypass, Wolters et al. noted that a majority of the patients were classified in ASA II (23%) and ASA III (73%), with only 4% in ASA IV and none in ASA classes I and V(Wolters et al., 2006). The higher the ASA score, the older were the patients, and the authors found no significant correlation between ASA classification and postoperative mortality or morbidity. The ASA classification is therefore problematic in predicting the fate of an individual patient, and its usefulness in that respect is limited.

The Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) risk-adjusted scoring system for predicting mortality in surgical patients was originally developed by Copeland et al. (Copeland, Jones and Walters, 1991) as a surgical audit scoring system between various hospitals. The mortality risk is predicted using a 12-factor, 4-grade physiological score (PS) and a 6-factor, 4-grade operative score (OS). The original POSSUM mortality regression equation has been modified by the Vascular Surgical Society of Great Britain and Ireland to produce a regression equation (V-POSSUM) that can be specifically applied to patients undergoing major vascular surgery (Copeland et al., 1993). The POSSUM score has been used to score patients with abdominal aortic aneurysm (AAA) repairs in both elective (Prytherch, Sutton and Boyle, 2001)(Shuhaiber et al., 2001) and ruptured cases (Jones, 1991, Lazarides et al., 1997). In the study by Volters et al. (Wolters et al., 2006)(Wolters et al., 2006), the POSSUM scoring was contradictory to the mortality observed, and the regression analysis in this respect did not turn out to be a significant predictor of postoperative mortality or morbidity. On the other hand, Mosquera et al. (Mosquera, Chiang and Gibberd, 2008) found a trend toward lowered risk-adjusted predicted mortality using V-POSSUM, but this benefit came from the general performance of surgery and did not predict the fate of individual patients.

There are a number of different indexes used as a means to evaluate surgical risks but which were originally planned for postoperative intensive care unit patients (APACHE (Knaus et al., 1981) SAPS (Le Gall, Loirat and Alperovitch, 1983). In vascular surgery, the focus of risk evaluations has been on AAA procedures, and the previously mentioned risk scoring systems have been used to estimate operative risk and predict outcome. Because of their complexity and the fact that they have not been developed for that purpose, there has been a need to find a model that is easy to calculate and use. Samy et al. (Samy, Murray and MacBain, 1994, Samy, Murray and MacBain, 1996) derived and validated a simple scale, the Glasgow Aneurysm Score (GAS), for risk stratification of patients undergoing elective and emergency open repair of AAA. It identified preoperative shock, myocardial dysfunction, renal impairment and cerebrovascular disease as significant factors in determining postoperative outcome (Samy, Murray and MacBain, 1994). In further studies by Biancari et al. (2003), the model was validated using data on 403 patients operated in a single hospital and again using the Finnvasc national database (Biancari et al., 2003, Biancari et al., 2003). In a systematic review of the current evidence predicting risk in elective AAA repair, Patterson et al. (Patterson et al., 2008) estimated GAS to be the most useful and consistently validated risk scoring system at present for risk prediction in open AAA repair. Drawbacks of the GAS are that it does not reliably identify individual high-risk patients due to a low positive predictive value

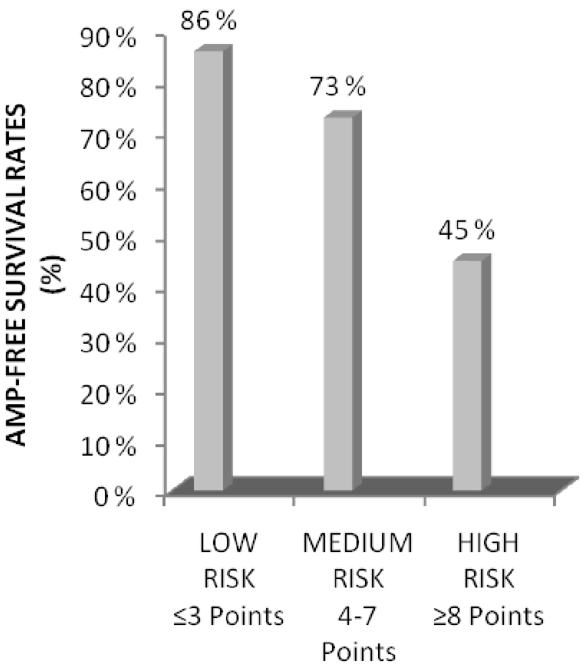
(Biancari, Hobo and Juvonen, 2006) and that it is consistently inaccurate when used to predict morbidity (Patterson et al., 2008).

1.6.2 Risk assessment in CLI

Since perioperative cardiac mortality and morbidity are the most frequently occurring adverse events in non-cardiac vascular surgery, the majority of the previously-mentioned risk indexes are focused on the evaluation of perioperative cardiac risk (Kertai et al., 2005, Eagle et al., 1989b). However, there is a strong relationship between perioperative cardiac and non-cardiac complications and subsequent mortality; almost half of the patients who experience cardiac morbidity develop other types on non-cardiac complications and mortality (Fleischmann et al., 2003). In addition, the currently available risk indexes estimate the risk of cardiac death rather than all-cause mortality, which may lead to inappropriate interpretations and underestimation of the factors increasing the risk of all-cause mortality (Kertai et al., 2005, Lauer et al., 1999).

1.6.3 The PIII risk score

Schanzer et al. (Schanzer et al., 2008) presented the PIII risk score model to predict amputation-free survival (AFS) using multi-centre data on surgical outcomes. The model included five independent predictors identified from the Project of Ex-Vivo graft Engineering via Transfection III (PREVENT III) database (Conte et al., 2006): dialysis-dependent renal failure (4 points), tissue loss defined as a non-healing ulcer or gangrene (3 points), advanced patient age ≥ 75 years (2 points), anaemia (hematocrit < 30, 2 points) and CHD (1 point) (Figure 5). The PIII risk score is meant to be a clinical tool for surgical decision-making, enabling physicians to generate a preoperative risk estimate that addresses an individual patient's likelihood of success or failure after surgical revascularisation. The PIII estimates amputation-free survival and does not predict mortality and morbidity. In the validation by Schanzer et al.(Schanzer et al., 2009), the PIII risk score was tested against 3,285 CLI patients who underwent a infrainguinal autogenous vein bypass in a multicentre study. PIII seemed to be a simple and reliable method to risk stratify CLI patients being considered for bypass into three distinct categories of expected amputation free-survival. (Schanzer et al., 2009).



	POINTS
DIALYSIS	4
TISSUELOSS	3
AGE ≥ 75	2
HCT ≤ 30%	2
CHD	1

Figure 5. PIII risk score card for CLI. (Modified from Shanzer 2008).

1.6.4 The Lee index and Customised Probability Model

The Customised Probability Model (CPM) presented by Kertai et al. (Kertai et al., 2005) estimates the risk of perioperative all-cause mortality. The model is a modification of the Lee index (Lee et al., 1999b) and meant to serve as a predictor of cardiac complications and perioperative all-cause mortality for patients undergoing vascular surgery. The model includes five of the six predictors from the original Lee index (high-risk type of surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease and renal dysfunction) associated with an increased risk of perioperative all-cause mortality. However, the risk associated with the type of elective vascular surgery as defined by the Lee index only differentiates high-risk procedures (abdominal aortic surgery) and low-risk procedures (infrainguinal bypass, carotid endarterectomy and aortobifemoral bypass). In CPM the type of surgery is redefined on the basis of timing (acute or elective), complexity and reported mortality rates, and the type of vascular surgery procedure is considered an important predictor of mortality (Kertai et al., 2005). CPM is the only model to pay attention to medication: If the patient has any of the risk factors described in CPM, β-blockers should be incorporated into the perioperative risk-reduction strategies (Boersma et al., 2001). Patients identified by clinical risk factors and non-invasive testing as being at high risk are often susceptible to considerable perioperative mortality despite β-blocker use (Boersma et al., 2001), and for these patients a combination of β-blockers and statins may offer additional prevention (Poldermans et al., 2003). Therefore, the CPM considers both β-blockers and statins in the risk score, suggesting that if, despite medication, the estimated probability of death remains high and there is a clear indication for coronary revascularisation independent of the need for vascular surgery, a coronary intervention should be considered (Kertai et al., 2005, Eagle et al., 2002). The role of β-blockers is controversial: in a systematic review and meta-analysis, Wiesbauer et al. showed that β-blockers reduce perioperative arrhythmias and myocardial ischemia but had no effect on myocardial infarction, mortality or the length of hospitalization(Wiesbauer et al., 2007). In a recent meta-analysis by Talati et al., β-blockers seemed to have a trade-off between a reduction in myocardial infarction and an increase in stroke, thus producing a troubling trend towards an increase in mortality (Talati et al., 2009).

1.6.5 The Finnvasc risk-scoring method

In a large study based on the Finnvasc registry (Salenius, 1992), independent predictors for 30-day postoperative mortality and major amputation were analyzed from the data on 3,925 infrainguinal surgical revascularisation procedures (Biancari et al., 2007). In this model diabetes, CHD, foot gangrene and urgent operation were risk factors that yielded 1 point each in the score. The 30-day postoperative mortality / major lower limb amputation rate increased significantly along with this additive risk score, as did also occur for the 30-day postoperative mortality and major lower limb amputation rates (Biancari et al., 2007). In this simple scoring method based on well-known risk factors, patients with three points had significantly higher postoperative mortality and/or limb loss. Recently, the scoring method has been validated with prospective data on 512 infrainguinal PTA revascularization procedures for CLI, and the method seemed to be useful in estimating the risk of immediate post-procedural mortality and/or major lower limb amputation also in patients undergoing infrainguinal PTA for CLI (Kechagias et al., 2008).

1.7 Invasive treatment of PAD and quality of life

Although the success of a particular intervention has traditionally been described in terms of graft patency and limb salvage, the primary goal for revascularisation procedures in the treatment of PAD is to improve the patient’s quality of life. However, published data seldom provide information on the ultimate effect of interventions on patients' quality of life. The TransAtlantic Inter-Society Consensus (Norgren et al., 2007) recommended that QoL instruments should be used in all clinical trials, but at present there is no established disease-specific questionnaire for QoL assessment for patients with CLI. The changes in ABI and walking distance are the basics values of postoperative evaluation for revascularisation procedure success, but they have proven to have relatively weak correlation with QoL (Currie et al., 1995, Whyman et al., 1996).

Two types of instruments are available to measure QoL: disease-specific and generic (Anderson, Aaronson and Wilkin, 1993). Generic instruments such as the Nottingham Health Profile (NHP) (Hunt and McEwen, 1980), the Short-Form 36 Health Survey (SF-36) (Ware and Sherbourne, 1992) and 15D (Sintonen, 1994) are applicable to a wide variety of populations. They address multidimensional aspects – such as physical functioning, emotion or mood, social functioning, role performance, pain and commonly performed daily activities (Klevsgard et al., 2002) – and have been used for and proven to have an acceptable degree of reliability in group-level comparisons. The NHP, however, seems to be better in discriminating the severity of ischemia and is thus more responsive in patients with CLI (Wann-Hansson et al., 2004). Disease-specific instruments such as the VASCUQOL (Vascular Quality of Life Questionnaire) (Morgan et al., 2001) and Intermittent Claudication Questionnaire (ICQ) (Chong et al., 2002) have been developed for claudication patients, including specific parameters related to overall symptoms and management in treadmill testing connected with ABI measurements.

2 AIMS OF THE STUDY

The aims of the present study were to investigate the risk factors of operative treatment and the impact of endovascular treatment of chronic lower limb ischemia in CLI. Furthermore, the devise models for identifying high-risk patients to minimise procedure-dependent mortality and morbidity were examined. The specific questions were:

1. Are there any differences in the grade and location of arterial stenosis between diabetics and non-diabetics with PAD?

2. What is the role of DM as a risk factor for surgery on CLI?

3. What is the impact of endovascular treatment of claudication and CLI on the quality of life?

4. Could GAS predict survival in surgical treatment of CLI?

3 PATIENTS AND METHODS

3.1 Does diabetes protect the femoral artery against atherosclerosis? (Study I)

The study group consisted of 60 non-diabetic and 38 diabetic patients with lower extremity disease and no previous vascular interventions. Patients were collected to the study in a prospective manner at the Central Hospital of Central Finland between November 1999 and September 2000. The patients were referred to the hospital because of suspected circulatory problems in their lower extremities. The anamnesis and the reason for hospitalisation were recorded. The patients were evaluated by measuring walking distance on a treadmill and the ankle-brachial index (ABI). Arterial lesions were investigated by digital subtraction angiography (DSA).

Each examination was subsequently evaluated by one experienced angiologist who had no previous information as to whether a patient was diabetic or non-diabetic. The scoring system used was modified from an article by Faglia et al. (Faglia et al., 2007). The extent of the stenosis in each vessel segment was determined visually and displayed numerically. The highest lumen reduction in each segment determined the score for the segment. This was 0 if the lumen was reduced to 50% or less at its narrowest point, 1 if the reduction was 50%–75%, 2 if the reduction was 76%–99% and 3 if there was a total occlusion. In the foot the score was 0 if there was at least one arterial trunk (i.e. dorsal or plantar artery) patent, and 1 if both were invisible.

3.2 Diabetes as an independent risk factor for early postoperative complications in critical limb ischemia (Study II)

Data on all vascular procedures performed in Finland during 1991–1999 were systematically collected into the national Finnvasc registry. All five university hospitals, all of the 16 central hospitals and the four largest district hospitals participated in the registry. The details of the Finnvasc protocol have been described elsewhere (Salenius, 1992). The protocol consisted of preoperative patient data such as risk factors and the indication for surgery, in addition to operative details such as urgency, procedure code and anatomy, graft, as well as data concerning the 30-day outcome including postoperative complications, re-operations and patency data. All arterial surgery, including endovascular interventions and access surgeries, were entered in the registry. One vascular surgeon in each hospital was responsible for data collection and the validity of the data. At the hospitals, information was recorded in paper form and sent to the central office where data were entered on a computer. The data includes a total of almost 40,000 surgical and endovascular procedures.

In the study, all 5,709 surgical procedures performed due to CLI were selected from the Finnvasc registry data. Critical ischemia was defined according to the Fontaine classification as F III or F IV, i.e. ischemic rest pain, non-healing ulcer or tissue defect or gangrene, irrespective of the distal ankle-brachial index (ABI) measured. Risk factors for perioperative death and morbidity were analysed with special emphasis on differences between diabetics and non-diabetics.

Logistic multiple regression was used to analyse the influence of factors affecting postoperative 30-day outcome. The independent factors analysed are presented in Table 2 and the dependent (30-day outcome) factors that were tested in Table 3.

In addition, analysis was carried out separately for both groups, the diabetics and non-diabetics, to find out if there were differences in the influence of various risk factors on 30-day mortality. The independent factors analysed were the same as in the analysis mentioned above, with diabetes as a discriminator. Of the 5,709 procedures, 2,508 were performed on diabetics (43.9%).

Age and sex	years, male/female
Cardiac risk	previously documented myocardial infarction and/or ongoing angina pectoris or previous coronary bypass surgery
Diabetes	hyperglycaemia requiring diet, oral medication or insulin treatment
Hypertension	medication for hypertension or arterial pressure >160/95 mmHg
Cerebrovascular disease	history of stroke or transient ischemic attacks
Pulmonary disease	asthma or chronic obstructive pulmonary disease
Renal failure	creatinine > 150 umol/L
Smoking	current smoker
Indication for surgery	divided in three categories: rest pain, ulceration, gangrene
Anatomic level and extent of the procedure	divided in 5 main categories: aortoiliac or femoral reconstruction, extra-anatomic reconstruction for central PAD, femoral endarterectomy including profundoplasty, femoropopliteal reconstruction, femorodistal reconstruction
Urgency of the procedure	(elective, urgent) and whether the procedure was primary or secondary

Table 2. Independent factors.

Cardiac complication	myocardial infarction or ischemia with ECG changes (electrogardiogram) and/or raised troponin levels
Cerebrovascular complication	stroke or transient ischemic attack (TIA)
Renal complication	renal failure with raised serum creatinine level from 150 umol/l up to irreversible renal insufficiency requiring dialysis
Respiratory complication	pulmonary embolism, pneumonia or pulmonary oedema
Superficial wound infection	local wound infection which was cured with local care and antibiotics and did not need revision or drainage in the operating room
Below-knee (BK) amputation	
Above-knee (AK) amputation	
Multi-organ failure (MOF)	
Acute occlusion of the graft or endarterectomised segment after surgery	

Table 3.The dependent (30-day outcome) factors.

3.3 Impact of endovascular treatment on clinical status and health-related quality of life (Study III)

A total of 61 consecutive patients and 64 limbs underwent a primary PTA (percutaneous transluminal angioplasty) procedure in a teaching hospital of an academic institution during a period of 18 months. Data were collected prospectively. Clinical criteria for categories of chronic limb ischemia were outlined according to Ahn and Rutherford (Ahn et al., 1993). The clinical grades I (claudication), II (ischemic rest pain) and III (tissue loss) account for the different natural histories of each group. ABI was used as a non-invasive haemodynamic assessment together with triplex scan evaluation performed immediately and one year after the PTA procedure. The quality of life was assessed using the Nottingham Health Profile (NHP) developed by Hunt and McEwen (Hunt and McEwen, 1980), and its Finnish version was employed in this study (Koivukangas P, Ohinmaa A, Koivukangas 1995). The NHP is a two-part instrument, and only part I was used. The 38 yes/no items reflect the patient's degree of distress within the domains of pain, physical mobility, emotional reactions, energy, social isolation and sleep. The answers are given as a score between 0 and 100 describing the degree of harm in each item. The NHP questionnaire was filled out before the PTA procedure as well as one month and one year after the procedure.

3.4 Predictors for the immediate and long-term outcome of a vascular surgical procedure (Study IV)

The data consisted of 157 consecutive patients who underwent an elective vascular surgical procedure in a teaching hospital between April 2002 and April 2003. The preoperative examination and data collection were performed by a vascular surgeon or vascular surgical fellow, and the ASA score was determined by an anaesthetist.

Patients were divided into three groups according to the indication for surgery: carotid, chronic limb ischaemia and abdominal aortic aneurysm procedures. The Glasgow Aneurysm Score (GAS) was calculated using the following formula: age in years + 7 (for myocardial disease) + 10 (for cerebrovascular disease) + 14 (for renal disease) (Samy, Murray and MacBain, 1994, Samy, Murray and MacBain, 1996). Myocardial disease refers to a previously documented myocardial infarction and/or ongoing angina pectoris. Cerebrovascular disease refers to all grades of stroke including TIA. Renal disease refers to a history of chronic and acute renal failure, and/or a serum creatinine level greater than 150 µmol/l at the time of surgery. Patients were divided into two GAS groups based on the study by Hirzalla et al. (Hirzalla et al., 2006): GAS <77 (GAS low) and GAS>=77 (GAS high).

A postoperative renal complication was defined as an increase in the serum concentration of creatinine or urea requiring medical treatment or dialysis. A postoperative cardiac complication was defined as a myocardial infarction (ECG changes or increased serum troponin level) or death due to cardiac causes, as well as postoperative cerebrovascular complications such as a TIA or stroke. Long-term mortality data for up to 5 years postoperatively were obtained from Statistics Finland.

3.5 Statistical methods

In all original articles the data were statistically analyzed using SPSS (Statistical Package for Social Sciences) software, and in Study I the Kolmogrov-Smirnov test was used to test the normality of the distributions of the variables. Differences in the mean values of the variables between diabetics and non-diabetics were analyzed by means of the Mann-Whitney test. Associations between pairs of variables were studied using the Chi-squared test or Spearman's correlation.

In Study II results were expressed as mean and standard deviation. Differences between means were tested for significance using two-tailed Student’s t-test. Comparison of proportions was performed using Pearson's χ^2 test or the Odds ratio. Multivariate analysis was performed using logistic regression. The p values less than 0.05 were considered significant.

In Study III mean values of the variables between claudication and CLI patients were compared using the independent samples t-test or the Mann-Whitney test. The means of the preoperative, 30-day follow-up and one-year follow-up values were compared using the dependent samples t-test or the Wilcoxon test and general linear models for repeated measures.

In Study IV data was expressed as mean value and standard deviation. The Chi-Square test, logistic regression as well as the Cox proportional hazards model and the Kaplan-Meier Survival Analysis were used in data analysis.

4 RESULTS

Table 4. Basic characteristics of the individual studies.

Study	***I***	***II***	***III***	***IV***
Subjects / Number of participants	98 consecutive patients *	Finnvasc, national registry: 5,709 CLI patients	61 consecutive patients **	157 consecutive patients***
Design	Prospective clinical study	Retrospective registry-based study	Prospective clinical study	Prospective clinical study
Aim of study	Investigation of the extent of atherosclerotic stenoses in different segments of the leg arteries	Evaluation of diabetes as a risk factor for post-operative major morbidity and mortality after surgery for CLI	Investigation on the impact of PTA on clinical status and health-related quality of life with claudication and CLI	Investigation of the risk factors for short- and long-term outcome after vascular surgical procedures
Methods	Scoring of arterial lesions on DSA	Multivariate analysis of preoperative risk factors	Clinical status: Fontaine classification and ABI Quality of life: NHP Outcome after procedure: Triplex scan evaluation	GAS predicting short- and long-term outcome
Results / Conclusions	Diabetics had fewer stenoses in the superficial femoral artery Diabetics had a tendency towards more diffuse atherosclerotic disease in crural arteries	Diabetes was not an independent risk factor for early post-operative mortality in CLI, as there was increased morbidity in diabetics associated with definitive risk factors	In claudication PTA resulted in an immediate improvement in the quality of life, but this effect seems to vanish in the long term. There was a subgroup of CLI patients in whom PTA led to a significant benefit in terms of limb salvage and quality of life	GAS had good predictive value for outcome after general vascular surgical procedures among low-risk patients (GAS < 77) For high-risk patients, due to its low predictive value for death, GAS yields limited value in clinical practice

* 11/1999 – 9/2000 Vascular Surgery Outpatient Clinic and Emergency Care Deparment of the Central Hospital of Central Finland

** 5/2002 – 1/2005 Vascular Surgery Outpatient Clinic of the Department of Vascular Surgery, Tampere University Hospital

*** 4/2002 – 4/2003 Vascular Surgery Outpatient Clinic of the Department of Vascular Surgery, Tampere University Hospital

4.1 Anatomical findings between diabetics and non-diabetics

Diabetics were referred to hospital because of more severe symptoms (foot ulcers or ischemic rest pain) than non-diabetics whose most usual reason for referral was claudication (Table 5). Walking distance ranged from 17 to 500 meters, with a mean value of 230 meters, and 28 patients were not able to take a treadmill test. Of these 28, 11 patients had substantial ulcers in the foot and five suffered from severe rest pain and not being able to walk. Furthermore, three patients had hemiplegic symptoms after a cerebral stroke and nine suffered from general weakness due to old age. ABI ranged from 0.23 to 1.01, with a mean of 0.62. In 21 cases, ABI had not been evaluated either because the patients had arrived in hospital from the emergency department or ABI could not been defined because of incompressible arteries.

	Diabetes		
Symptom (N/%)	**No**	**Yes**	**Total**
Claudication	47 (78.0)	13 (34.2)	60 (61.2)
Ulcers	6 (10.0)	12 (31.6)	18 (18.4)
Rest pain	4 (6.7)	9 (23.7)	13 (7.1)
Other*	3 (5.0)	4 (10.5)	7 (7.1)

*Cold feet
swelling
skin pigmentation
suspected failure in circulation

Table 5. Reason for referral for further examinations.

In the scoring analysis, statistically significantly fewer (score value 1,55 vs. 1,00 P=0,037) stenoses were found in the superficial femoral artery in diabetics than in non-diabetics. Although a tendency towards more diffuse changes in crural arteries was found, no statistically significant differences were observed in other segments of the lower leg arteries apart from the femoral arteries. At the aorto-iliac level, there were no significant differences between patient groups.

4.2 Risk factors and survival from the procedures

The early (30-day) complications in diabetics and non-diabetics after surgery for CLI are presented in Table 6, the multivariate analysis of the risk factors for early postoperative death in Table 7, and adjusted odds ratios with a 95% CI from multiple logistic regression for postoperative complications in a 30-day follow-up in diabetics and non-diabetics in Figure 6.

In multivariate analysis, aortofemoral reconstruction (OR, 4.0), preoperative cardiac risk factor (OR, 3.1), primary surgery (OR, 2.0), renal insufficiency (OR, 1.9), urgent surgery (OR, 1.7), and age (OR, 1.3) were found to be independent factors for postoperative death, whereas diabetes was not an independent risk factor for 30-day mortality after the procedure (OR, 1.3; 95% confidence interval [CI], 0.95-1.75; P=0.8) (Table 8).

In multivariate analysis of the 30-day follow-up for diabetics compared to non-diabetics, diabetes was found to be an independent risk factor for postoperative BK amputation (OR, 1.7), cardiac complications (OR, 1.5), and superficial wound infection (OR, 1.3) (Figure 6).

Multivariate analysis was also used to evaluate whether there were differences in the predictive value of various pre- and intra-operative factors on 30-day outcome between diabetics and non-diabetics. Aortofemoral reconstruction (OR 2.5), urgent surgery (OR 2.0), male sex (OR 2.0), renal insufficiency (OR 1.9), cardiac risk factor (OR 1.7) and age (OR 1.4) were independent risk factors for early postoperative mortality in diabetics. In non-diabetics, independent risk factors for early postoperative mortality were aorto-iliac or aorto-femoral reconstruction (OR 4.5), cardiac risk factor (OR 3.6), primary surgery (OR 2.6) and extra-anatomic bypass for central peripheral arterial occlusive disease (OR 2.3) (Table 8).

	Total		Diabetics		Non-diabetics		P-value
	n	%	n	%	n	%	
Superficial wound infection	731	12.8	395	15.7	336	10.5	<0.001
Below-knee amputation	270	4.7	164	6.5	106	3.3	<0.001
Cardiac complication	401	7.0	221	8.8	180	5.6	<0.001
Cerebrovascular complication	94	1.6	53	2.1	41	1.3	<0.05
Renal complication	70	1.2	40	1.6	30	0.9	<0.05
Death	221	3.9	111	4.5	110	3.4	=0.05
Acute graft occlusion	561	9.8	230	9.2	331	10.3	n.s.
Respiratory complication	171	3.0	69	2.8	102	3.2	n.s.
Above knee amputation	194	3.4	87	3.5	107	3.3	n.s.
MOF	24	0.4	10	0.4	14	0.4	n.s.

n.s. = nonsignificant

Table 6. Early (30-day) complications in diabetics and non-diabetics after surgery for critical limb ischemia.

	OR		95% CI
Aortoiliac or -femoral reconstruction[1]	4.0	**	(2.5-6.4)
Cardiac risk	3.1	**	(2.3-4.4)
Primary compared to secondary surgery	2,0	*	(1.3-3.1)
Renal insufficiency	1.9	*	(1.2-2.9)
Extra-anatomic bypass for central PAOD[1]	1.8	*	(1.2-2.9)
Urgent compared to elective surgery	1.7	**	(1.3-2.4)
Age (per 10 years)	1.3	**	(1.1-1.4)
Diabetes	1.3		(0.95-1.7)
Male sex	1.3		(0.9-1.7)
Gangrene compared to rest pain	1.3		(0.8-2.0)
Cerebrovascular risk	1.2		(0.8-1.7)
Pulmonary risk	1.2		(0.8-1.8)
Femorodistal reconstruction[1]	1.2		(0.8-1.9)
Ulcer compared to rest pain	1.1		(0.8-1.6)
Femoral endarterectomy[1]	1.0		(0.5-1.8)
Smoking	0.9		(0.6-1.3)
Hypertension	0.8		(0.6-1.1)

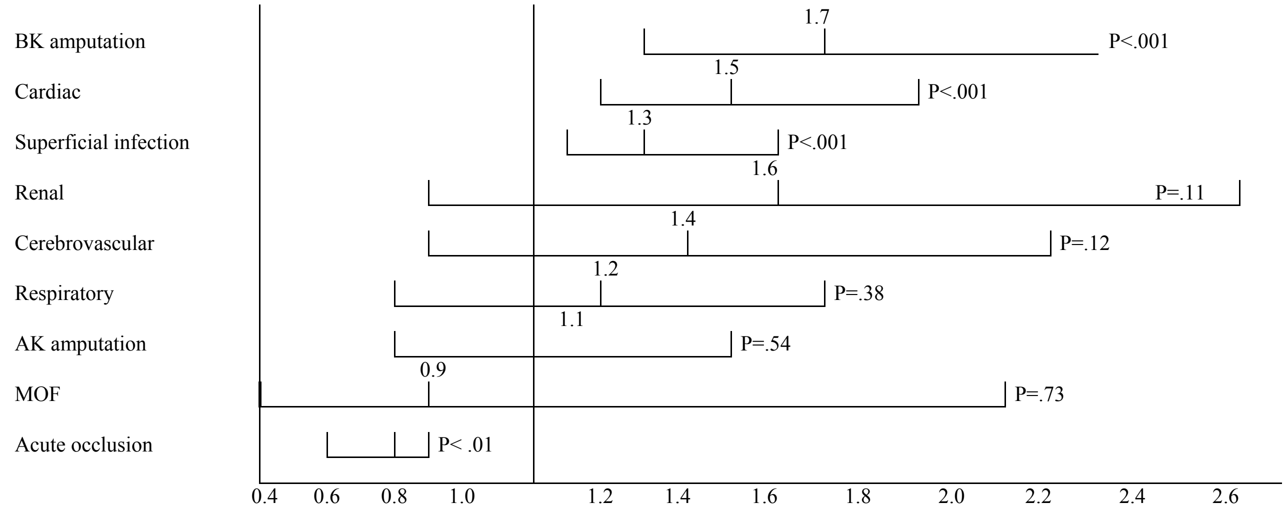
[1] Compared to femoropopliteal reconstruction
*P<.05
**P≤.001

Table 7. Multivariate analysis of the risk factors for early (30-day) postoperative death.

	Diabetics			Non-diabetics		
	RR		(95% CI)	RR		(95% CI)
Aortoiliac or -femoral reconstruction [1]	2.5	*	(1.1-5.9)	4.5	**	(2.4-8.3)
Urgent compared to elective surgery	2.0	*	(1.3-3.2)	1.4		(0.9-2.3)
Male sex	2.0	*	(1.3-3.0)	0.8		(0.5-1.3)
Renal insufficiency	1.9	*	(1.1-3.3)	1.9		(0.9-4.1)
Cardiac risk	1.7	**	(1.4-2.2)	3.6	**	(2.3-5.6)
Age (per 10 years)	1.4	**	(1.2-1.7)	1.0		(0.7-1.2)
Femoral endarterectomy [1]	1.7		(0.8-3.6)	0.4		(0.1-1.4)
Primary compared to secondary surgery	1.5		(0.8-2.7)	2.6	*	(1.3-5.2)
Pulmonal insufficiency	1.4		(0.8-2.6)	1.1		(0.7-1.9)
Femorodistal reconstruction [1]	1.4		(0.8-2.3)	1.0		(0.5-1.9)
Gangrene compared to rest pain	1.2		(0.7-2.2)	1.2		(0.6-2.5)
Ulcer compared to rest pain	1.1		(0.7-1.9)	1.2		(0.8-1.8)
Extra-anatomic bypass for central PAOD [1]	1.1		(0.6-2.4)	2.3	*	(1.3-4.2)
Hypertension	1.0		(0.7-1.5)	0.7		(0.5-1.1)
Smoking	1.0		(0.5-1.7)	0.9		(0.6-1.4)
Cerebrovascular disease	1.0		(0.8-1.3)	1.4		(0.9-2.4)

[1] Compared to femoropoplitel reconstruction
*P<.05
**P<.001

Table 8. Multivariate analysis of the significance of preoperative factors for early (30-day) postoperative mortality in diabetics and non-diabetics.



BK=Below knee
AK=Above knee
MOF=Multi organ failure

[1] Factors that were evaluated in the logistic regression analysis:

Age	
Sex	
Diabetes	Hyperglycemia requiring diet, oral medication or insulin treatment
Hypertension	Medication for hypertension or arterial pressure >160/95 mmHg
Cardiac risk factor	Previously documented myocardial infarction and/or ongoing angina pectoris or previous coronary artery bypass surgery
Cerebrovascular risk factor	History of stroke or transient ischemic attacks
Pulmonal risk factor	Asthma or chronic obstructive pulmonary disease
Renal risk factor	History of chronic and acute renal failure, and/or serum level of urea over 20 mmol/l and/or creatinine serum level greater than 150 micromol/l
Smoking	Current smoker or smoking during the previous 5 years
Preoperative severity of ischemia	Rest pain vs. ulcer vs. gangrena
Anatomic level of reconstruction and extent of operation	Femoropopliteal reconstruction vs. femoral endarterectomy vs. distal reconstruction vs. extra-anatomic reconstruction for aortoiliac occlusion vs. aortoiliac-aortofemoral reconstruction
Urgency of the reconstruction	Elective vs. emergency operation
Primary vs. secondary procedure	

[2] Postoperative adverse events

BK amputation	Below-knee amputation
Cardiac	EKG changes and/ or elevated troponin levels
Renal	Renal failure with raised serum creatinine level from 120 mmol/l up to irreversible renal insufficiency requiring dialysis
Superficial infection	Local wound infection which cured with local care and antibiotics, and which did not need revision or drainage in operating room
Cerebrovascular	Stroke or TIA
Respiratory	Pulmonal embolism, pneumonia or pulmonal edema
AK amputation	Above knee amputation
MOF	Multiorgan failure
Death	

Figure 6. Adjusted Odds ratios with 95% CI from multiple logistic regression[1] for postoperative complications[2] in 30-day follow-up in diabetics compared to nondiabetics.

4.3 Impact of endovascular treatment on clinical status and health-related quality of life

4.3.1 Claudication

All limbs underwent triplex ultrasound immediately after the PTA, and 20/30 (66.7%) of the treated areas were open with 0%–50% residual stenosis, with 10 limbs having residual stenosis of 51%–99%. None of the 30 segments treated were occluded. All patients were invited to and 26 attended a 30-day clinical follow-up. At 30 days, 22/26 (84.6%) of the patients with a total of 27 treated limbs had no claudication, and 3/26 (11.5%) had claudication. The mean ABI in patients who underwent 30-day follow-up increased from the preoperative 0.63 to 0.84. One patient who did not attend the 30-day control but did attend the one-year control with no claudication, the treated segment open with 0%–50% restenosis and an ABI of 1.02 in the treated limb. A total of 24 patients and 27 treated limbs underwent the one-year follow-up, including a clinical control visit and triplex ultrasound: 21/24 (87.5%) had no claudication, and 3/24 (12.5%) had claudication which had been present throughout the one-year follow-up period. Triplex ultrasound showed that 17/27 (63.0%) controlled sections were open with 0%–50% restenosis, 9/27 (33.3%) were observed to have 51% – 99% restenosis, and 1/27 (3.7%) PTA segment was occluded. The mean ABI in these patients was 0.63 preoperatively and 0.85 at one year's follow-up. Three patients did not attend the control examination: one was in very poor general condition and did not wish to attend the follow-up, and two did not come to the one-year control visit despite several calls, the reason for which remained unknown.

4.3.2 Critical limb ischemia

All patients underwent triplex ultrasound one day after the PTA – 13/34 (38.2%) segments were open with residual stenosis of 0%–50%, in 20/34 (58.8%) there was residual stenosis of 51%–99%, and one of the treated sections occluded immediately. Twenty-seven of the 34 patients underwent a 30-day clinical follow-up. At 30 days, 6/34 (18.6%) patients were asymptomatic, 9/34 (26.5%) had claudication, one (2.9%) suffered from rest pain, and 11/34 (32.4%) had a persisting ulceration. The mean ABI in patients who underwent the 30-day follow-up increased from 0.54 to 0.67.

Thirteen patients underwent the one-year follow-up including a clinical control visit and a triplex-ultrasound examination. None of them suffered from critical limb ischemia at that time: eight patients were asymptomatic and five had claudication. At the one-year triplex ultrasound control, six patients had restenosis of 0%–50% in the PTA-treated arterial segment, and seven had 51%–99% restenosis. No occlusions were observed. Among the 13 patients who underwent the one-year follow-up, ABI had increased from the preoperative 0.56 to 0.86 at one year's follow-up. Twenty-one patients did not attend the one-year follow up: seven patients had died, six underwent amputation, and bypass surgery was performed on five patients. Three patients did not observe the invitation to attend the control examination, one of whom was in institutional health care and in very poor conditions at the time and for two patients the reason for not attending remained unresolved.

4.3.3 Quality of life

The quality of life was measured preoperatively, at 30 days' follow-up and at one year's follow-up. There were only 14 claudicants and 7 CLI patients who answered the questions on all occasions. In the domains of energy and pain, claudicants seemed to improve their value after one month, but these changes were not quite statistically significant, and at one year's follow-up, the scores were significantly worse than at one month's follow-up. For both claudicants and CLI patients, the mean value for energy was even worse at one year's follow-up than preoperatively, but the difference is not statistically significant. For CLI patients, improvement was seen in the domain of pain, which continued at both follow-up points, and the difference was statistically significant between the one-year follow-up and the preoperative score. In the domain of sleep, there was significant improvement for claudicants at one month's follow-up, and it continued until the one-year follow-up was concluded. For CLI patients, the improvement was not so clear, but they also reported improved values at one year's follow-up in comparison to the preoperative score. Among claudicants, the domain of physical mobility was significantly improved at the one-month point when compared to the preoperative value, but at the one-year follow-up, the improvement had nearly disappeared and the score was no longer significantly better than preoperatively.

4.4 Predictors for the immediate and long-term outcome of a vascular surgical procedure

The most common indication for the procedure was chronic limb ischemia (61.5%, 95/157), followed by carotid disease (26.1%, 41/157) and abdominal aortic aneurysm (13.4%, 21/157).

The 30-day mortality rate was 2.5% (4/157). The only independent risk factor for 30-day mortality was the renal risk factor (OR 20.2). None of the patients in the GAS low group died, and the mortality rate in the GAS high group was 10.7% ($p=0.03$).

During the 5-year period following the procedure, 40.8% (64/157) of the patients died. In the Cox proportional hazards model, independent predictors for long-term mortality included the renal risk factor (OR 3.9), the cardiac risk factor (OR 2.3), age (OR 1.5) and procedure type (carotid surgery as a reference category: OR for an infrainguinal procedure 3.5 and for infrarenal aorta 3.3). Twelve-month survival for the patients in the GAS low and GAS high groups was 98.6% and 78.6%, respectively ($p<0.0001$), the respective 5-year figures being 76.7% and 44.0% ($p=0.0001$). All four patients with renal disease, cardiac disease and cerebrovascular disease died within 2 years of the procedure.

5 DISCUSSION

5.1 Distribution of atherosclerotic lesions in patients with PAD

The early angiography-based studies carried out in the 1960s (Haimovici, 1967)(Conrad, 1967) already disclosed that the atherosclerotic process may exhibit a great variety of lesions in the lower extremities. However, a study by Strandness et al. (Strandness, Priest and Gibbons, 1964) reported that the pattern of occlusive involvement of the major arteries is distinctly different in diabetic than in non-diabetic patients, the former having a higher incidence of involvement in the arteries below the knee, and the incidence of involvement in the femoro-popliteal level is the same as for non-diabetics. The concept of a more distal distribution of atherosclerotic occlusions in diabetic patients dates back to these early studies which did not report the incidence and severity of plaques and stenoses. Later on in the 1990s, as digital subtraction angiography was established as a routine method for the diagnosis of severe PAD, several studies re-evaluated the anatomic pattern of PAD (Ciavarella et al., 1993, Faglia et al., 1998). These studies confirm the more frequent involvement of calf arteries in diabetic patients, and this phenomenon seemed to be particularly evident in diabetics with foot ulcers (Faglia et al., 1998).

The present study confirms the earlier findings of the tendency in diabetics to have a more diffuse form of PAD in their calf arteries than non-diabetics, while the superficial femoral artery seemed to remain less attenuated compared to patients without diabetes. It is unknown why the distribution of atherosclerosis differs between patients with and without diabetes. In our patient material, diabetics had severe symptoms (ulcers) more often than non-diabetics upon arrival at the hospital. This is probably due to the diminished sense of pain in the neuropathic foot, but as to whether the more progressed disease affects the present DSA findings remains speculative. However, a considerable part of our patients suffered from a very severe form of PAD, and as many as 28 out of 98 patients were not able to perform the treadmill test due to their inability to walk at all, which was attenuated in the group of diabetic patients.

One possible bias in the present study is that the number of participants is low, which can cause a certain skew as to the matching of the study groups. However, the numbers of patients in the original referred articles were 77 (Strandness, Priest and Gibbons, 1964) and 189 (Haimovici, 1967), and in Conrad's study, only 20 extremities amputated for gangrene were included (Conrad, 1967).

5.2 Diabetes as a risk factor in operative treatment of critical limb ischemia

There are over 500,000 diabetics in Finland, and it has been estimated that their number will double during next 10–15 years (Onkamo et al., 1999) (Duodecim Diabetes Käypä hoito Duodecim 2007;123(16):1985-6). Combined with the aging of the population, this will have a great impact on vascular surgery. The association between DM and postoperative mortality as well as cardiac morbidity is strong, but the role of DM as an independent risk factor has been unclear. Several studies (Eagle et al., 1996, Eagle et al., 1989a, Lee et al., 1999a)(Biancari et al., 2007) have considered DM an independent risk factor for perioperative mortality in non-cardiac surgery, in association with silent ischemia, low ejection fraction and compensated heart failure. However, other studies (Axelrod et al., 2002, Hamdan et al., 2002) have found that DM alone does not explain the higher mortality or cardiac morbidity rates associated with major vascular procedures. In our study based on the Finnvasc registry of 5,709 operations, DM was not an independent risk factor for early postoperative mortality in CLI, but morbidity in diabetics was increased and associated with old age, male sex, known CHD and urgent surgery.

The reason for the higher morbidity and mortality among diabetics is often widespread atherothrombotic disease, and it has been estimated that approximately 75% of all deaths in diabetics are due to cardiovascular causes (Bierman, 1992). Another well-accepted observation is that patients undergoing major vascular operations are at significant risk of perioperative cardiac morbidity and mortality, and especially patients with DM have been considered to have an elevated risk of cardiac complication (Eagle et al., 2002, Axelrod et al., 2002). The present unadjusted complication rates suggested that patients with DM had a significantly higher rate of postoperative deaths, cardiac complications as well as cerebrovascular and renal complications, in addition to above-knee amputations and superficial wound infections. This incremental risk, however, mostly depended on the higher levels of specific co-morbidities among diabetic patients, such as hypertension, hyperlipidemia, congenital heart disease and renal insufficiency as well as more severe ischemia as an indication for the procedure. After adjusting these differences, we found no significant differences in early postoperative cerebrovascular and renal complication rates, but the rate of postoperative cardiac complications remained significantly higher in diabetics.

Although DM does not appear to have an independent impact on postoperative mortality rates, diabetics have several prominent problems affecting their outcome after vascular surgery procedures, including an increased risk to develop postoperative wound infections and to undergo below-knee amputation. Diagnosing a diabetic foot is difficult because of masking by neuropathy which causes a delay in diagnosis and the initiation of effective treatment. If there is extensive tissue loss, especially with deep infection, amputation can be inevitable despite successful revascularisation.

In one Finnish study, limb salvage was not achieved in 8% of the patients with CLI despite successful revascularisation, as they were referred to vascular surgery too late (Eskelinen et al., 2003). In our studies, the indication for the operation or DSA in the diabetic group was gangrene or ulceration more often than in non-diabetics, which emphasised the problem and delay in the diagnosis of a diabetic foot.

Femorodistal bypasses are performed significantly more often for diabetics than for non-diabetics, which is in accordance with the more distal locations of arterial lesions in diabetics than in non-diabetics. More distal and severe arterial occlusions are also one probable reason for the higher 30-day below-knee amputation rate following revascularisation that was seen in our study. DM also remained an independent risk factor for early below-knee amputation when the differences in the preoperative stage of ischemia were taken to into consideration. One in three graft occlusions led to amputation within one month in both diabetics and non-diabetics, and the acute graft occlusion rate was equal in both groups, which further emphasises the independent role of DM in increasing the risk of amputation. In cases in which the graft was patent at 30 days, significantly more diabetics than non-diabetics underwent amputation, which supports the notion that in diabetics, reconstruction is often performed late and that diabetics more commonly must undergo amputation due to major tissue loss, despite successful revascularisation.

The weakness of the study is that registry data is always somewhat inaccurate. Especially the registration of risk factors may be unreliable (Lepantalo et al., 1994, Kantonen et al., 1997). However, if a patient has diagnosed diabetes, it is well-documented in the patient’s records. Therefore, diabetes is probably one of the most reliably registered risk factors. Kantonen et al. audited the reliability of the Finnvasc data (Kantonen et al., 1997), and one of the most accurate types of data were postoperative complications. The number of patients is high in the current study, and in spite of certain inaccuracies, registry data can be used in the study, and we believe the results to be reliable.

5.3 Endovascular treatment of claudication and CLI as well as impact on QoL

The role of endovascular treatment of PAD has increased significantly during the last five years. Even at the end of the last decade, the general opinion was that PTA should not be considered as a primary treatment for CLI except in extraordinary circumstances (Parsons et al., 1998), but the enthusiasm toward PTA due to improvements in endovascular technology and expertise has led to the suggestion that PTA should be the first choice for most of the patients requiring lower-extremity revascularisation (Nasr et al., 2002) (Adam et al., 2005). According to the BASIL trial with patients presenting with severe limb ischemia due to infra-inguinal disease and suitable for surgery and angioplasty, both the PTA-treated and the surgically treated groups were associated with broadly similar outcomes in terms of amputation-free survival, and in the short term, surgery was more expensive than angioplasty (Adam et al., 2005). However, with the high failure and re-intervention rate associated with PTA, the apparently improved durability and reduced re-intervention rate of the bypass method favours surgery for patients expected to live more than two years and who are relatively fit (Adam et al., 2005).

The fact is that one of the primary goals of vascular surgical interventions besides limb salvage and graft patency is to improve the patients' quality of life. The impact of PTA on the QoL of claudicants has been recognized (Currie et al., 1995) (Chetter et al., 1998), but QoL studies with CLI patients are based mainly on bypass surgery treatments (Klevsgard et al., 2002)(Wann-Hansson et al., 2005), with few studies reporting an over six-month follow-up (Wann-Hansson et al., 2005).

One problem is that although the TransAtlantic Inter-Society Consensus (Norgren et al., 2007) recommended that QoL should be evaluated in clinical trials, there are at present no established disease-specific questionnaires for QoL assessment in patients with CLI. There are, however, two generic instruments, the NHP and SF-36, which have been evaluated on the basis of validity, reliability and responsiveness analyses by Klevsgård et al. (Klevsgard et al., 2002) as suitable for detecting changes in QoL as regards the treatments for CLI.

The technical success of PTA procedures in our study was 100%, and postoperative complications were rare. Furthermore, the clinical success for claudication patients was good: Only one PTA-treated segment was occluded at one year's follow-up, and more than 80% of the patients were free of claudication. As a whole, the present study demonstrated the poor outcome of CLI patients with high mortality and morbidity rates; however, one third of CLI patients survived with no critical ischemia at one year's follow-up. The patients with rest pain seemed to have received more benefits, whereas the outcome was poorer in legs with tissue loss.

A recent study on peripheral angioplasty for CLI produced findings that support our results. In a study on infra-popliteal angioplasty for critical limb ischemia, Giles et al. (Giles et al., 2008) suggested that an attempt at PTA may be indicated as an alternative to primary amputation for patients who are not candidates for bypass, although restenosis, re-intervention or amputation rates are naturally high. Although the overall survival rates of the 163 patients included in the study were 80%, 63% and 54% at 1, 2, and 3 years, respectively, the authors achieved a limb salvage rate of 84% at 3 years for this very challenging group of patients (Giles et al., 2008). In a study by Faglia et al. (Faglia et al., 2007), PTA proved effective in avoiding major amputation if re-canalisation occurred in at least one tibial artery down to the foot, but in a few of their patients, re-canalisation of the peroneal artery alone was not sufficient to avoid major amputation. In their analysis, the risk of major amputation remained very high if PTA was performed only in the femoral-popliteal segment, thus leaving crural segments obstructed (Faglia et al., 2007).

The outcome of unreconstructed CLI is very poor in terms of both survival and limb salvage (Norgren et al., 2007). In a study on the outcome of 105 unreconstructed CLI patients and 136 legs, the limb salvage rates were 81%, 70% and 54% at 1, 3 and 12 months, respectively, with the respective survival rates amounting to 93%, 77% and 46% (Lepantalo and Matzke, 1996). Therefore, attempting PTA procedures seems justified in this special group of CLI patients in order to avoid major amputation and, particularly, if this will have sufficient impact on the patient's QoL.

Filling out the NHP questionnaire independently proved difficult or even impossible for many of our patients especially among the CLI patients who are older and whose more serious illness causes varying levels of disability. For a significant number of the patients, the questions involving the domains of social isolation and emotional reactions caused embarrassment, and the results in that domain were not reliable. The questions in the domains of energy, pain and mobility were more tolerated, and patients found them easier to answer. The sensitivity of the NHP domains of pain and physical mobility, associated with the severity of ischemia, has been proven earlier in other studies (Wann-Hansson et al., 2004). Because there were only 11 CLI patients remaining after one year of follow-up who were able to answer the questions, the differences between the mean values did not reach statistical significance. However, in this group of patients, the scores in the domain of pain improved postoperatively, and the improvement continued up to the one-year control. In the domain of physical mobility, the improvement for claudicants was clear and statistically significant, but this improvement disappeared during one-year follow-up, and for the CLI group, there were no changes in the QoL value of mobility. The explanation for this is that PAD patients have several other co-morbidities effecting mobility, and especially CLI patients with severe limb ischemia stay relatively immobile although leg salvage is achieved, and the aging of the patient groups certainly has an adverse effect.

5.4 Predictors for the immediate and long-term outcome of a vascular surgical procedure

Although CLI patients have several co-morbidities and their risk profile is extremely high with regard to surgical procedures, there are no simple scoring methods available at present for this specific group of patients. The GAS has appeared to be a good predictor of outcome after elective open repair of an AAA, and it is also simple to use as an instrument for preoperative risk stratification (Biancari et al., 2003) – these advantages attracted us to test the method on elective vascular surgery patients.

Our study showed that GAS has predictive value for the prognosis after vascular surgery procedures, and because the survival form infrarenal aortic and infrainguinal procedures was similar, the use of GAS in surgical procedures for CLI needs to be validated externally. Based on our study, the estimation is that GAS selects low-risk patients well and is useful in identifying high-risk patients, but the drawback is that, on the individual level, suitability for operations must be considered separately for the high-risk group. The number of patients included in the current study is too low to make far-reaching conclusions, but the findings may be useful in evaluating individual patients in everyday clinical work.

6 CONCLUSIONS

1. Diabetics had fewer stenoses in the superficial femoral arteries, and they had a tendency towards more diffuse atherosclerotic changes in their crural arteries compared to nondiabetics.
2. Diabetes alone was not an independent risk factor for early postoperative mortality after lower limb revascularization for CLI, but the morbidity seemed to be increased in diabetics in association with old age, male sex, coronary artery disease and renal insufficiency, as well as urgent surgery. Diabetes was an independent risk factor for early postoperative myocardial ischemia, BK amputation and wound infection.
3. PTA resulted in an immediate improvement in the quality of life in claudicants, but this effect was not seen in the long term. In CLI there was a subgroup of patients who gained significant benefits in terms of both limb salvage and the quality of life.
4. A low GAS value (<77) predicted low mortality after surgery, while a higher risk score was clearly associated with higher mortality. However, due to its low predictive value, GAS is not accurate in attempting to identify patients who will not survive surgery even in the high-risk patients (GAS>77).

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9 ORIGINAL PUBLICATIONS

Angiology and Vascular Surgery Vol 11 No 1/2005

DOES DIABETES PROTECT THE FEMORAL ARTERY AGAINST ATHEROSCLEROSIS?

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ABSTRACT

Background: **To compare the extent of angiographically detected stenoses in different segments of the lower leg arteries in diabetics and nondiabetics.**

Methods: **The study group consisted of 60 nondiabetic and 38 diabetic patients with lower extremity disease and no previous vascular interventions. Arterial lesions were analysed by digital subtraction angiography (DSA). The patients were evaluated by walking distance and ankle-brachial index (ABI) and the reason for hospitalization was recorded.**

Results: **Statistically significantly fewer stenoses were found in the superficial femoral artery in diabetics than in nondiabetics. Although a tendency to more diffuse changes in crural arteries was found, no statistically significant difference were found in other segments of the lower leg arteries apart from the femoral arteries.**

Conclusions: **Judging from the present results there are fewer angiographically detectable stenoses in the superficial arteries in diabetics than nondiabetics.**

Keywords: Diabetes, peripheral arterial occlusive disease, angiography

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INTRODUCTION

Diabetes is an important independent risk factor for peripherial atherosclerotic disease(1). Previous studies have demonstrated that diabetics differ from other individuals in the location of occlusive atherosclerotic disease. Cast studies and angiographic examinations have shown diabetics to have more stenotic disease in the calf vessels than nondiabetics, particularly in the peroneal and posterior tibial arteries. Furthermore, the arteriosclerotic process is more diffuse in the diabetic group (2,3,4). In foot vessels diabetics seem to have even fewer stenoses than nondiabetics (3) and surprisingly, fewer stenotic lesions have been found in some lower leg arteries in diabetics than nondiabetics (5,6). If this is indeed, the case some factor in diabetics or their lower leg arteries must be assumed to protect their superficial femoral arteries against atherosclerosis.

The purpose of the present pilot study was to establish whether there really are fewer stenoses in some lower leg arteries in diabetics than in nondiabetics

MATERIALS AND METHODS

We evaluated all vascular patients during the period November 23, 1999 to September 4, 2000 at our vascular surgery outpatient clinic and first aid department. The patients referred because of suspected circulatory problems in their lower extremities. DSA was performed on all those who were considered to need invasive treatments. Patients who had previously undergone vascular surgical or radiological interventions were excluded from the study. The final cohort comprised 98 patients, their age varying between 34 and 90 years, mean age 68.9 years. Furthermore, 60 (61.2 %) of them were nondiabetics and 38 (38.8 %) diabetics. Four patients in the nondiabetic group had no DSA available for their legs, and two for their their feet. One of the patients had thrombosis of the distal aorta (Leriche syndrome) and the rest had total obstructions in upper part of the lower extremity arterial trunk. Consequently, the concentration of the contrast agent was too low for analysis of the distal part of the arterial trunk. Diabetes had previously been verified in health center or hospital, and the diagnoses were assesed via the medical record of internal disease. The duration of the disease could not be sufficintly reliably determined in all cases. (Table1).

Table 1. Characteristics of patiens.

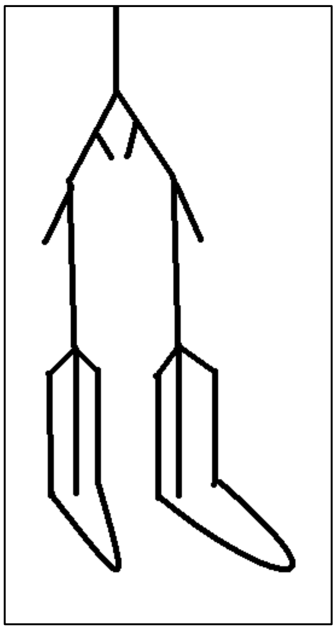
	Diabetes		
	No	Yes	Total
Number of patients	60	38	98
Male/female	28/35	24/14	52/46
Age (range)	43-89	34-90	34-90
Mean	68.5	69.5	68.9
Median	69.5	71.5	70.0

Walking distance was measured by treadmill test. The patients walked 500 meters at a speed of 3,6 km per hour, and if the exercise caused any claudicational pain intense enough to stop the walking, this was noted.

ABI was performed by Imex Lab 9000^{R} test. The test uses pressure cuffs to measure the left and right systolic brachial pressures simultaneusly, and photopletysmography (PPG) probes to sense the blood flow.

DSA (Siemens Polytron/Angiostar) was performed on all patients in aortic flush manner (Ultravist 300 mgI/ml). Right femoral access, under local anesthesia, was the method used. Each study was later evaluated by the same experienced angiologist who had no previous information as to whether a patient was diabetic or nondiabetic. The extent of the stenosis in each vessel segment was determined visually and displayed numerically (Figure 1). The scoring system used was modified from an article by Faglia and associates. (7). The highest lumen reduction in each segment determined the score for the segment. This was 0 if the lumen was reduced to 50% or less at its narrowest point, 1 if the reduction was 50-75 %, 2 if the reduction was 76-99 % and 3 if there was a total occlusion. In the foot the score was 0 if there was at least one arterial trunk (i.e. dorsal or plantar artery) patent, and 1 if both were invisible.

Figure 1. The illustration of the scoring system.



SUPRAINGUINAL SEGMENT
Distal aorta
A.iliaca communis
A.iliaca externa
A.femoralis communis

FEMORO-POPLITEAL SEGMENT
A.femoralis profunda
A.femoralis superficialis
A.poplitea

LEG AND FOOT
A.tibialis anterior
A.fibularis
A.tibialis posterior
A. plantaris pedis
A. dorsalis pedis

SCORE:
0= < 50% STENOSIS
1= 50 - 75 % STENOSIS
2= 75 - 99 % STENOSIS
3= OCCULUSION
FOOT 0 = A.DORSALIS PEDIS OR A. PLANTARIS PEDIS OPEN
FOOT 1 = NO VASCULAR LUMEN

The data were statistically analyzed using SPSS (Statistical Package for Social Sciences). To test the normality of the distributions of the variables the Kolmogrov-Smirnov test was used. Furthermore, since the variables were not normally distributed, and as in some cases there were only a few observations in a group, nonparametric methods were used. Because the tests applied are designed for independent observations, both legs of the same person were not studied concurrently. The leg with more severe symptoms was chosen for the main study, but also the other leg of diabetics and nondiabetics was compared. Differences in the mean values of the variables between diabetics and nondiabetics were analyzed by Mann-Whitney test. Associations between pairs of variables were studied using the Chi-squared test or Spearman's correlations.

RESULTS

Claudication was the most common reason for referral for further examinations in hospital in both groups. However, foot ulcers were almost as common in diabetics. Rest pain, cold feet, failures in foot circulation, swelling and discolored skin were mentioned less frequently (Table 2).

Walking distance ranged from 17 to 500 meters, mean value 230 meters; 28 patients were not able to take a treadmill test. There were 11 patients who had substantial ulcers in the foot, and five suffered from severe rest pain, not being able to walk. Furthermore, three patients had hemiplegia after cerebral infarction, and nine suffered from general weakness due to old age. There were no significant differences between diabetics and nondiabetics in the walking distance achieved (Table 3).

ABI ranged from 0,23 to 1,01, the mean value being 0,62. In 21 cases ABI had not been evaluated, either because the patients had arrived in hospital from the first aid department, or it could not be defined because of uncompressible arteries. There were no significant differences in ABI values between diabetics and nondiabetics. The ABI value was missing or could not be taken slightly more often in the diabetics group (Table 3).

In scoring analysis there were no significant differences in distal aorta, iliaca and femoralis communis levels. At femoro-popliteal levels the angioscore value was lower in the diabetic group mainly due to the femoralis superficialis, which appeared to have significantly fewer stenoses in the diabetic group.

In calf vessels there were no significant differences in total score between the two groups when all three arteries were measured concurrently. Nondiabetics seemed to have fewer changes in single arteries, but the grade of stenosis was somewhat higher. Diabetics tended to evince minor changes more often in all three arteries, and thus their atherosclerotic disease was evidently more diffuse. Nondiabetics were likely to have a total stenosis of the tibialis anterior slightly more often than diabetics.
In foot arteries there were no significant differences between the two groups (Table 4).

Table 2. Reason for referral for further examinations.

Symptom (N/%)	Diabetes		
	No	Yes	Total
Claudication	47	13	60
%	78,3	34,2	61,2
Ulcers	6	12	18
%	10.0	31.6	18.4
Rest pain	4	9	13
%	6,7	23,7	13,3
Other	3	4	7
%	5,0	10,5	7,1
cold feet			
swelling			
skin pigmentation			
failure in circulation			

Table 3. Walking distance and ankle-brachial index

	Diabetes		
	No	Yes	Total
Walking distance			
Mean	231	227	230
Median	200	162	188
Min/Max	20 – 500	17 – 500	17 – 500
Missing	11	17	28
ABI			
Mean	0.61	0.63	0.62
Median	0.60	0.62	0.60
Min/Max	0.23 – 1.01	0.25 – 0.99	0.23 – 1.01
Missing	7	14	21

Table 4. The summation of the scoring analyze.

	Diabetes		
	No	Yes	P
Aortofemoral segment			
(N)	60	38	
Mean	0,83	0,37	0,068
Median	0,00	0,00	
Min/Max	0/6	0/4	
Distal aorta			
(N)	60	38	
Mean	0,08	0,03	0,599
Median	0,00	0,00	
Min/Max	0/3	0/1	
A.Iliaca communis – A.femoralis communis			
(N)	60	38	
Mean	0,75	0,34	0,070
Median	0,00	0,00	
Min/Max	0/3	0/3	
A.femoralis – A.Poplitealis sement			
(N)	60	38	
Mean	0,75	1,95	0,024*
Median	3,00	2,00	
Min/Max	0/6	0/7	
A.femoralis profunda			
(N)	60	38	
Mean	0,32	0,37	0,877
Median	0,00	0,00	
Min/Max	0/3	0/3	
A.femoralis superficialis			
(N)	60	38	
Mean	1,55	1,00	0,037*
Median	2,00	0,50	
Min/Max	0/3	0/3	
A.poplitea			
(N)	60	38	
Mean	0,87	0,58	0,265
Median	0,00	0,00	
Min/Max	0/3	0/3	
Leg and foot			
(N)	54	38	
Mean	4,69	5361	0,170
Median	6,00	6,00	
Min/Max	0/10	0/10	
A.tibialis ant.			
(N)	58	38	
Mean	1,66	1,79	0,758
Median	2,50	2,00	
Min/Max	0/3	0/3	
A.fibularis			
(N)	58	38	
Mean	1,09	1,53	0,113
Median	0,00	2,00	
Min/Max	0/3	0/3	
A.tibialis post.			
(N)	58	38	
Mean	1,76	2,13	0,238
Median	3,00	3,00	
Min/Max	0/3	0/3	
Foot			
(N)	54	38	
Mean	0,22	0,16	
Median	0,00	0,00	
Min/Max	0/1	0/1	

*statistically significant difference

DISCUSSION

There are over 180 000 diabetic patients in Finland, almost 90 % of them suffering from non - insulin dependent diabetes mellitus. In Finland the incidence of type 1 diabetes has remained highest in the world (8) and the prevalence of NIDDM is relatively high (9). Over 11 % of the total expenses of health care are attributable to diabetes and its complications. In treatment the major proportion of expenses is due to heart and vascular diseases (10). According to the Finnish national vascular registry (FINNVASC), diabetes is estimated to be in 24,9% of cases a risk factor for patients treated surgically or endovascularly for peripheral vascular diseases (11). In a recent study from FINNVASC the data showed that diabetes mellitus and renal insufficiency increased the relative risk of amputations and mortality when evaluated by early results of endovascular treatment of chronic critical ischemia (12). Diabetics are believed to have a so-called ”small vessel disease” at arteriolar level, not amenable to surgical reconstruction. The belief persists and causes delay in adequate treatment for these patients. The prevalence of atherosclerotic occlusive disease appears to be approximately five times higher among patients with NIDDM, and the risk of arterial occlusive disease of the lower extremeties is also high when compared to nondiabetics (13).

In many previous cast or angiographic studies of diabetics with arterial occlusive disease, the symptoms of patients with lower extremity disease have been very severe. For example, cast studies have been made on amputated legs (3), and all patients in a study by Ciavarella and associates (5) had critical limb ischemia. In the present study, the severity of the symptoms varied more from suspected lower leg extremity arterial disease to foot ulcers and rest pain.

DSA is considered the golden standard in the diagnosis of vascular disease. It has certain disadvantages, not always showing patent distal vessels because of proximal stenoses or due to timing problems compared to the latest methods of magnetic resonance angiography (MRI) (14,15). The availability of MRI-based methods is as yet inadequate but their role in visualizing vascular diseases is certain to expand in the future.

In our patient material diabetics had severe symptoms (rest pain, ulcers) more often than non-diabetics upon arrival at the hospital. This is probably due to the diminished sense of pain in the neuropathic foot, resulting in underestimation of the disease, and thus in harmful delay in the initiation of adequate treatment.

Angiographic findings evinced no significant differences at distal aorta, iliaca and femoralis communis levels. At femoro-popliteal level diabetics had significantly fewer stenoses than nondiabetics. Smoking has previously been connected to proximal atheroscerotic disease (5) but the reliability of patients’ reports of smoking habits has turned out to be poor and hence history of smoking is not included in this report. In calf vessels and foot arteries we found no significant differences in total score between the two groups of patients, but the atherosclerotic disease seems to be more diffuse in the calf vessels of diabetics.

To conclude, DSA could not confirm all previous reported differences between these two patient groups. In the present pilot study of 38 diabetics and 60 nondiabetics statistically significantly (p = 0.037) fewer angiographic stenoses were found in the superficial femoral arteries of diabetics as against nondiabetics. If these findings are confirmed in a larger cohort, it would be interesting to clarify why diabetes protects the femoral artery from atherosclerosis.

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Diabetes as an independent risk factor for early postoperative complications in critical limb ischemia

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Objective: **The purpose of this study was to evaluate the significance of diabetes mellitus as a risk factor for postoperative major morbidity and mortality after surgery for critical lower limb ischemia (CLI).**

Subjects: **A national vascular registry (Finnvasc)– based survey included 5709 operations for CLI from 1991through 1999. Of these operations, 2508 (44%) were performed on diabetics. Tissue loss was the indication for surgery in 77% of diabetics and in 52% of nondiabetics. The proportion of femorodistal bypasses was 43% in diabetics and 24% in nondiabetics, whereas the proportion of reconstructions for aortofemoral arterial occlusive disease was 16% in diabetics and 34% in nondiabetics.**

Results: **Thirty-day mortality was 4.5% in diabetics and 3.4% in nondiabetics (P = .05). The rate for early below-knee amputation was 6.5% in diabetics and 3.3% in nondiabetics (P < .001). Independent factors for postoperative death were aortofemoral reconstruction (odds ratio [OR], 4.0), preoperative cardiac risk factor (OR, 3.1), primary surgery (OR, 2.0), renal insufficiency (OR, 1.9), urgent surgery (OR, 1.7), and age (OR, 1.3). Diabetes was an independent risk factor for postoperative below-knee amputation (OR, 1.7), cardiac complications (OR, 1.5), and superficial wound infection (OR, 1.3). There was an inverse association between diabetes and acute graft occlusion (OR, 0.8). Independent risk factors for early postoperative mortality in diabetes were aortofemoral reconstruction (OR, 2.5), urgent surgery (OR, 2.0), male gender (OR, 2.0), renal insufficiency (OR, 1.9), cardiac risk factor (OR, 1.7), and age (OR, 1.4). In nondiabetics independent risk factors for early postoperative mortality were aortofemoral reconstruction (OR, 4.5), cardiac risk factor (OR, 3.6), primary surgery (OR, 2.6), and extra-anatomic bypass (OR, 2.3).**

Conclusions: **Diabetes was not an independent risk factor for early postoperative mortality in CLI as there was an increased morbidity in diabetics associated with old age, male gender, known coronary artery disease, and renal insufficiency, as well as urgent surgery. As diabetics have increased proclivity for these factors, special attention needs to be paid to their preoperative assessments. (J Vasc Surg 2004;40:761-7.)**

The issue of the role of diabetes mellitus (DM) as a risk factor for vascular surgery is important because a large proportion of vascular surgical patients have DM. In the future, their number will increase due to the aging of population.[1,2] This is particularly true in patients with critical lower limb ischemia (CLI), ie, legs with threatened viability. Cardiovascular events are the main reason for perioperative mortality and morbidity after vascular surgery, and it has been suggested that DM further increases the risk.[3,4] There is an unquestionable association between diabetes and immunologic dysfunction, which is supposed to expose diabetics to infections.[5] Diabetes is also associated with renal and cerebrovascular complications and worse outcome of vascular operations, including risk of major amputation after infrainguinal surgery [6,7]; yet contradictory data exist as well.[8,9] In a study of outcome following femorotibial reconstruction, Luther and Lepäntalo[8] showed that patency, leg salvage, and survival were lower for diabetics than for nondiabetics, but this difference was entirely caused by low patency and leg salvage rates in diabetic women. Akbari et al[9] showed that DM does not influence late mortality, graft patency, or limb salvage rates after lower extremity arterial reconstruction.

The aim of the present study was to use data from a nationwide 9-year registry-based study to analyze the significance of diabetes as a risk factor for early postoperative mortality and morbidity in vascular reconstructions.

MATERIAL AND METHODS

Systematic data collection of all vascular procedures into national Finnvasc registry was started 1991 in Finland. The details of Finnvasc protocol have been described elsewhere by Salenius et al.[10] The protocol consisted of preoperative patient data, including risk factors and the indication for surgery; operative details, such as urgency, procedure code, and anatomy, graft material; as well as data concerning the 30-day outcome, including postoperative complications, reoperations, and patency. The overall number of recorded variables was over 200. All arterial surgery, including endovascular

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Table I. Demographic data and preoperative risk factors of the study patients

	Total	*Diabetics*	*Nondiabetics*	P
Mean age (SD)	71.4 (10.8)	70.5 (11.0)	71.7 (10.5)	<.001
Male:female (%)	50 : 50	51 : 49	58 : 42	<.001
Hyperlipidemia*	7.6	8.4	7.0	<.05
Hypertension†	37.2	41.7	33.7	<.001
Cardiac‡	50.7	55.9	46.6	<.001
Cerebrovascular§	14.9	15.7	14.2	ns
Pulmonal‖	11.3	8.3	13.7	<.001
Renal¶	7.2	11.0	4.0	<.001
Smoking**	29.5	16.8	39.4	<.001

***ns,* Nonsignificant.
*Serum concentration of cholesterol >6.5 mmol/L or of tryglycerids >2.0 mmol/L.
†Medication for hypertension or arterial pressure >160/95 mm Hg.
‡Previously documented myocardial infarction and/or ongoing angina pectoris.
§All grades of stroke including transient ischemic attacks.
‖Asthma or chronic obstructive pulmonary disease.
¶History of chronic and acute renal failure, and/or serum level of urea over 20 mmol/L, and/or creatinine serum level greater than 150 μmol/L. Current smoker.

interventions and access surgery, were registered in the registry. During the period from 1991 to 1999 all 5 university hospitals, all of the 16 central hospitals, and the 4 largest district hospitals participated in the registry. In each hospital, there was 1 vascular surgeon responsible for data collection and validity of the data. In hospitals information was recorded in paper form and sent to central office in Tampere, where data were entered into the computer using Paradox 4.0 software. Data for a total of almost 40,000 surgical and endovascular procedures are included in the database.

In the present study, all surgical procedures performed for CLI were selected for the analyses. Critical ischemia was defined according to Fontaine classification as F III or F IV, ie, ischemic rest pain, nonhealing ulcer or tissue defect, or gangrene irrespective of the distal ankle-brachial index (ABI). Risk factors for perioperative death and morbidity were analyzed with special emphasis on differences between diabetics and nondiabetics.

Logistic multiple regression was used to analyze the influence of factors affecting postoperative 30-day outcome. Analyzed independent factors were:

- Age
- Gender
- Cardiac risk factor: previously documented myocardial infarction and/or ongoing angina pectoris or previous coronary bypass surgery
- Diabetes: hyperglycemia requiring diet, oral medication, or insulin treatment
- Hypertension: medication for hypertension or arterial pressure >160/95 mm Hg
- Cerebrovascular disease: history of stroke or transient ischemic attacks
- Pulmonary disease: asthma or chronic obstructive pulmonary disease
- Renal failure: creatinine > 150 umol/L
- Smoking: current smoker
- Indication for surgery, divided into the following 3 categories: rest pain, ulceration, and gangrene
- Anatomic level and extent of the procedure, divided into the following 5 main categories: aortoiliac or femoral reconstruction, extra-anatomic reconstruction for central peripheral arterial occlusive disease (PAOD), femoral endarterectomy including profundoplasty, femoropopliteal reconstruction, and femorodistal reconstruction
- Urgency of the procedure (elective, urgent) and whether procedure was primary or secondary

Dependent (30-day outcome) factors that were analyzed included the following:

- Mortality
- Cardiac complication: myocardial infarction or ischemia with electrocardiogram changes and/or raised troponin levels
- Cerebrovascular complication: stroke or transischemic attack
- Renal complication: renal failure with raised serum creatinine level from 150 umol/L up to irreversible renal insufficiency requiring dialysis
- Respiratory complication: pulmonary embolism, pneumonia, or pulmonary edema
- Superficial wound infection: local wound infection which was cured with local care and antibiotics and did not need revision or drainage in operating room
- Below-knee (BK) amputation
- Above-knee (AK) amputation
- Multiorgan failure
- Acute occlusion of the graft or endarterectomized segment after the surgery

In addition, separate analyses were done for each group, diabetics and nondiabetics, to find out if there were

Table II. Indications for the operation in diabetics and nondiabetics

	Diabetics		*Nondiabetics*		*Total*	
	n	%	*n*	%	*n*	%
Rest pain	582	23.2	1543	48.2	2125	37.9
Ulceration	1485	59.2	1408	44.0	2893	51.6
Gangrena	441	15.7	250	7.8	691	10.5
Total	2508	100	3201	100	5709	100

Table III. The type of operation for critical limb ischaemia in diabetics and nondiabetics

	Total		*Diabetics*		*Nondiabetics*		
	n	%	*n*	%	*n*	%	P
Aortoiliac or femoral reconstruction	574	10.1	128	5.1	446	13.9	<.001
Extra-anatomic bypass for aortoiliac PAOD	899	15.7	274	10.9	625	19.5	<.001
Femoral endarterectomy*	491	8.6	196	7.8	295	9.2	ns
Femoropopliteal bypass	1610	28.2	712	28.4	898	28.1	ns
Femorodistal bypass	1850	32.4	1078	43.0	772	24.1	<.001
Other	285	5.0	120	4.8	165	5.2	ns
	5709	100.0	2508	100.0	3201	100.0	

ns, Nonsignificant.
*Including profundoplasty.

differences in the influence of various risk factors on 30-day mortality. Analyzed independent factors were the same as those listed previously, with diabetes as a discriminator.

The total number of operations for critical limb ischemia from 1991 through 1999 was 5709; of them 2508 were performed on diabetics (43.9%). Diabetics had significantly more hypertension, hyperlipidemia, and cardiac and renal involvements than nondiabetics, whereas smoking and pulmonary insufficiencies were more unusual among diabetics (Table I).

The most common manifestation of CLI was ulceration in 2893 patients (51.6%), followed by rest pain in 2125 patients (37.9%) and gangrene in 691 patients (10.5%). Diabetics more often had ulceration or gangrene as an indication compared with nondiabetics (Table II). The most common procedure in diabetics was femorodistal bypass (43.0%) whereas femoropopliteal bypass was most frequent in nondiabetics (28.1%). The proportion of femorodistal bypasses was higher in diabetics than in nondiabetics (43.0% and 24.1 %, respectively) whereas the proportion of reconstructions for aortoiliac arterial occlusive disease was lower in diabetics compared with nondiabetics (16.0 % and 33.4 %, respectively) (Table III).

Statistical analysis. Results were expressed as mean (standard deviation). Differences between means were tested for significance by using the 2-tailed Student *t* test. Comparison of proportions was performed by using the Pearson χ^2 test or calculating the odds ratio (OR). Multivariate analysis was performed by using logistic regression. *P* values <.05 were considered significant. Data analysis was carried out by using the SPSS/Win version 11.0.

RESULTS

30-day mortality after the procedure was 3.9%. The most common complication was superficial wound infection (12.8%), followed by acute graft occlusion (9.8%) and cardiac complication (7.0%) (Table IV). BK amputation was performed in 4.7% and AK amputation in 3.4% within 30 days of the procedure. In diabetics, 37.4% of patients whose graft occluded immediately after vascular surgery underwent early amputation compared with 32.6% of nondiabetics (not significant). The 30-day amputation rate in patients whose graft was open was 7.3% in diabetics compared with 3.7% in nondiabetics ($P < .0001$)

In multivariate analysis aortofemoral reconstruction (OR, 4.0), preoperative cardiac risk factor (OR, 3.1), primary surgery (OR, 2.0), renal insufficiency (OR, 1.9), urgent surgery (OR, 1.7), and age (OR, 1.3) were found to be independent factors for postoperative death (Table V). Diabetes was not an independent risk factor for 30-day mortality after the procedure (OR, 1.3; 95% confidence interval [CI], 0.95-1.75; $P = .08$). In multivariate analysis, diabetes was found to be an independent risk factor for postoperative BK amputation (OR, 1.7), cardiac complications (OR, 1.5), and superficial wound infection (OR, 1.3) (Fig 1). There was an inverse association between diabetes and acute graft occlusion (OR, 0.8).

Logistic regression modeling was also used to evaluate if there were differences between diabetics and nondiabetics in the predictive value of various pre- and intraoperative factors for 30-day outcome. Aortofemoral reconstruction (OR, 2.5), urgent surgery (OR, 2.0), male gender (OR, 2.0), renal insufficiency (OR, 1.9), cardiac risk factor (OR,

Table IV. Early (30-day) complications in diabetics and nondiabetics after surgery for critical limb ischemia

	Total		Diabetics		Nondiabetics		
	n	%	*n*	%	*n*	%	P
Superficial wound infection	731	12.8	395	15.7	336	10.5	<0.001
Below-knee amputation	270	4.7	164	6.5	106	3.3	<0.001
Cardial complication	401	7.0	221	8.8	180	5.6	<0.001
Cerebrovascular complication	94	1.6	53	2.1	41	1.3	<0.05
Renal complication	70	1.2	40	1.6	30	0.9	<0.05
Death	221	3.9	111	4.5	110	3.4	=0.05
Acute graft occlusion	561	9.8	230	9.2	331	10.3	ns
Respiratory complication	171	3.0	69	2.8	102	3.2	ns
Above-knee amputation	194	3.4	87	3.5	107	3.3	ns
MOF	24	0.4	10	0.4	14	0.4	ns

ns, Nonsignificant; *MOF,* multiorgan failure.

Table V. Multivariate analysis of the risk factors for early postoperative death

	Odds ratio	95% CI
Aortoiliac or aortofemoral reconstruction*	4.0†	(2.5–6.4)
Cardiac risk	3.1†	(2.3–4.4)
Primary compared to secondary surgery	2.0‡	(1.3–3.1)
Renal insufficiency	1.9‡	(1.2–2.9)
Extra-anatomic bypass for central PAOD*	1.8‡	(1.2–2.9)
Urgent compared with elective surgery	1.7†	(1.3–2.4)
Age (per 10 y)	1.3†	(1.1–1.4)
Diabetes	1.3	(0.95–1.7)
Male gender	1.3	(0.9–1.7)
Gangrena compared with rest pain	1.3	(0.8–2.0)
Cerebrovascular risk	1.2	(0.8–1.7)
Pulmonary risk	1.2	(0.8–1.8)
Femorodistal reconstruction*	1.2	(0.8–1.9)
Ulcer compared with rest pain	1.1	(0.8–1.6)
Femoral endarterectomy*	1.0	(0.5–1.8)
Smoking	0.9	(0.6–1.3)
Hypertension	0.8	(0.6–1.1)

*Compared to femoropopliteal reconstruction.
†$P \leq .001$.
‡$P < .05$.

1.7), and age (OR, 1.4) were independent risk factors for early postoperative mortality in diabetics. In nondiabetics independent risk factors for early postoperative mortality were aortoiliac or femoral reconstruction (OR, 4.5), cardiac risk factor (OR, 3.6), primary surgery (OR, 2.6), and extra-anatomic bypass for central peripheral arterial occlusive disease (OR, 2.3) (Table VI).

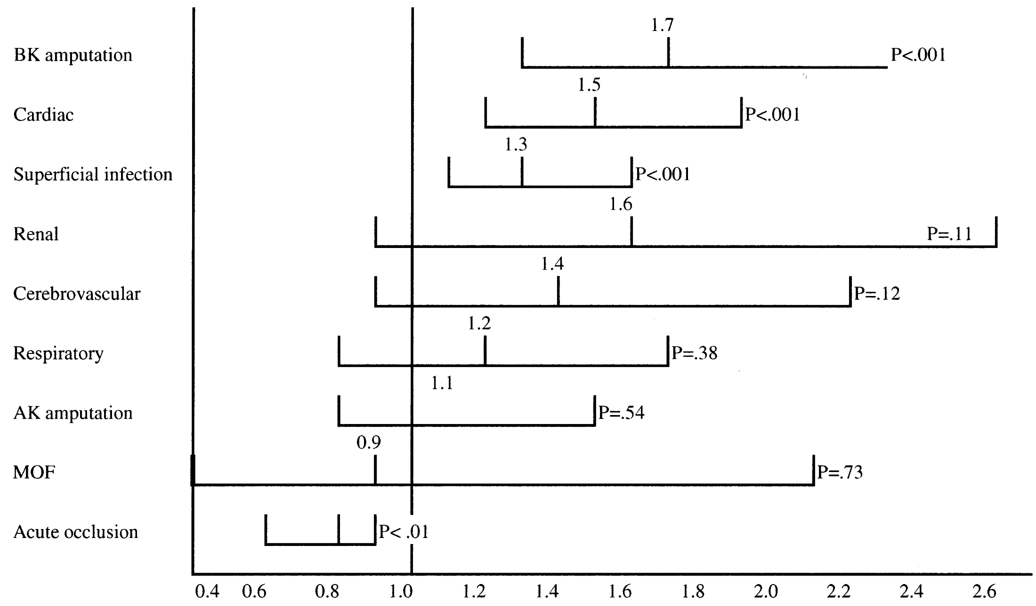
DISCUSSION

This registry-based study used Fontaine classification for CLI. Systematic implementation of more objective criteria might be impossible in a population-based study. Furthermore, the use of pressure criteria would skew the differences between diabetics with nondiabetics, as diabetics are apt to have mediasclerosis and pseudohypertension.

The association between DM and postoperative mortality and cardiac morbidity is strong, but the role of DM as an independent risk factor has been unclear. Eagle et al[11,12] and Lee et al[13] considered DM as an independent risk factor for perioperative mortality in non-cardiac surgery, associating with silent ischemia, low ejection fraction, and compensated heart failure. In a registry-based study including 6565 various vascular surgical procedures, including lower extremity revascularizations, carotid, or aortic procedures, Hamdan et al[14] found that diabetes alone did not explain a higher mortality or cardiac morbidity rate associated with major vascular procedures. Axelrod et al[15] had similar findings, concluding that DM did not appear to be an independent risk factor for postoperative mortality. These earlier studies included various types of vascular procedures, which may have had a confounding effect on the results. Our study included only vascular procedures due to critical limb ischemia, making the study population more homogeneous, with a higher propensity for coronary artery disease.[3]

This survey was based on a large registry, which might give rise to certain uncertainty as to the accuracy of the material. The audit of Finnvasc registry has been published twice, by Lepäntalo et al[16] in 1996 and Kantonen et al[17] in 1997. In the latter evaluation, the data were audited by comparing the originally recorded Finnvasc forms and the set of rerecorded forms filled in later. It was found that the most inaccurate data were preoperative risk factors and operation code; the overall data agreement with the original data was 93 %, with a range among participating hospitals of 81% to100 %. The number of missing cases was 19%. The validity of Finnvasc data could be thus considered acceptable for a nationwide registry despite the fact that the data thereafter might be skewed because some hospitals have been unable to participate in the registry during the past 2 to 3 years.

In our material, there were significant differences between diabetics and nondiabetics in preoperative risk factors. The overrepresentation of coronary artery disease, hypertension, renal disease, and hyperlipidemia is easy to understand because hypertension and hyperlipidemia are 2 risk factors leading to metabolic syndrome, and renal disease is often a complication of DM. The proportion of smokers was smaller among diabetics than nondiabetics in our study as in several other studies.[9,18,19] Probably due to



Adjusted odds ratios with 95% CI from multiple logistic regression for postoperative complications in 30-day follow-up in diabetics compared to nondiabetics. *BK*, Below knee; *AK*, above knee; *MOF*, multi organ failure.

difference in smoking habits, nondiabetics also had higher rate of chronic obstructive pulmonary disease. Because of clear differences in preoperative risk profile, it was important to adjust factors by using multivariate analysis. For example, Akbari et al[8] found significantly higher in-hospital mortality in diabetics compared with nondiabetics after lower-limb revascularization (0.9% vs 4.2%). However, their data were not adjusted for different risk factors between the groups (eg, diabetics were 4 years younger that nondiabetics). In our study, multivariate analysis enabled control of the skewness of the comparisons between the diabetics and nondiabetics.

The reason for higher morbidity and mortality among diabetics is often widespread atherothrombotic disease. According to Bierman[20], about 75% of all deaths in diabetics are due to atherothrombotic disease. Another well-accepted observation is that patients undergoing major vascular operations are at significant risk for perioperative cardiac morbidity and mortality.[15] Patients with DM have been considered to have an elevated risk of cardiac complications compared with nondiabetics, which has necessitated a lower threshold for cardiac stress testing.[12]

Unadjusted complication rates suggested that patients with diabetes had a significantly higher rate of postoperative deaths, cardiac complications, and cerebrovascular and renal complications, as well as AK amputations and superficial wound infection. Most of this incremental risk, however, depended on the higher levels of specific comorbidities among diabetic patients, such as hypertension, hyperlipidemia, congenital heart disease, and renal insufficiency, as well as more severe ischemia as an indication for the procedure. After adjusting these differences, there were no significant differences in early postoperative cerebrovascular and renal complication rates. In our multivariate analysis DM alone was not an independent risk factor for postoperative mortality either. After adjustment of preoperative and intraoperative factors in multivariate analysis, the rate of postoperative cardiac complications remained significantly higher in diabetics. Although the prevalence of subclinical coronary artery disease in the diabetic population is high, it may also be clinically silent in this population. Autonomic neuropathy in diabetics may interfere with the perception of cardiac pain and myocardial ischemia.[21,22]

Silent ischemia may also have an impact on postoperative incidence of diagnosed myocardial ischemia. Thus, in some cases, cardiac complication may remain undiagnosed in diabetics. On the basis of registry data, it is naturally impossible to suggest the number of possible undiagnosed cases with silent ischemia.

Although DM does not appear to have independent impact on postoperative mortality rates, diabetics have several notable problems affecting their outcome after vascular surgery procedures. The diagnosis of diabetic foot is still difficult because of masking by neuropathy. That causes delay in diagnosis and beginning of effective treatment. Severity of preoperative tissue loss influences the outcome of limb after reconstruction. If there is extensive tissue loss, especially with deep infection, amputation can be inevitable despite successful revascularization. Indeed, the high amputation rate, especially among diabetics with open grafts, might be sign of the severity and extent of the disease.

In a Finnish study, despite successful revascularization, limb salvage was not obtained in 8% of the patients with CLI, as they were referred to vascular surgery too late.[23] In our study, the indication for the operation in diabetic group was gangrene or ulceration more often than in nondiabetic

Table VI. Multivariate analysis on the significance of preoperative factors for early postoperative mortality in diabetics and nondiabetics

	Diabetics		*Nondiabetics*	
	RR	*(95% CI)*	*RR*	*(95% CI)*
Aortoiliac or aortofemoral reconstruction*	2.5†	(1.1–5.9)	4.5‡	(2.4–8.3)
Urgent compared with elective surgery	2.0†	(1.3–3.2)	1.4	(0.9–2.3)
Male gender	2.0†	(1.3–3.0)	0.8	(0.5–1.3)
Renal insufficiency	1.9†	(1.1–3.3)	1.9	(0.9–4.1)
Cardiac risk	1.7‡	(1.4–2.2)	3.6‡	(2.3–5.6)
Age (per 10 y)	1.4‡	(1.2–1.7)	1.0	(0.7–1.2)
Femoral endarterectomy*	1.7	(0.8–3.6)	0.4	(0.1–1.4)
Primary compared to secondary surgery	1.5	(0.8–2.7)	2.6†	(1.3–5.2)
Pulmonal insufficiency	1.4	(0.8–2.6)	1.1	(0.7–1.9)
Femorodistal reconstruction*	1.4	(0.8–2.3)	1.0	(0.5–1.9)
Gangrena compared with rest pain	1.2	(0.7–2.2)	1.2	(0.6–2.5)
Ulcer compared with rest pain	1.1	(0.7–1.9)	1.2	(0.8–1.8)
Extra-anatomic bypass for central PAOD*	1.1	(0.6–2.4)	2.3†	(1.3–4.2)
Hypertension	1.0	(0.7–1.5)	0.7	(0.5–1.1)
Smoking	1.0	(0.5–1.7)	0.9	(0.6–1.4)
Cerebrovascular disease	1.0	(0.8–1.3)	1.4	(0.9–2.4)

RR, Risk ratio; *PAOD,* peripheral arterial occlusive disease.
*Compared to femoropopliteal reconstruction.
†$P < .05$.
‡$P < .001$.

group, where rest pain without tissue damage was the most common indication. Incorrect distal pressure measurements may also mislead in the diagnosis of critical leg ischemia. Femorodistal bypasses are performed significantly more often in diabetics compared with nondiabetics, which is in accordance with more distal locations of arterial lesions in diabetics than nondiabetics. More distal and severe arterial occlusive disease is also one probable reason for the higher 30-day BK-amputation rate following revascularization that was seen in our study. Diabetes also remained an independent risk factor for early BK amputation when the differences in preoperative stage of ischemia were taken into consideration. One of 3 graft occlusions led to amputation within 1 month in both diabetics and nondiabetics. The acute graft occlusion rate was equal in both groups, which further emphasizes the independent role of diabetes in increasing the risk of amputation. In cases in which the graft was patent at 30 days, significantly more diabetics than nondiabetics underwent amputation. This supports the suggestion that in diabetics reconstruction is often performed too late, and that diabetics more commonly must undergo amputation due to major tissue loss, despite successful revascularization.

An interesting finding in our study was that urgent operations were associated with higher mortality in diabetics but not in nondiabetics. One reason might be the concurrent severe infection more often associated with emergency surgery in diabetics than in nondiabetics. Also, in urgent cases preoperative patient evaluation, risk factor assessment, and treatment may be more incomplete than in elective cases. This might further increase the number myocardial ischemic complications, especially in diabetics with undiagnosed silent ischemia and glycemic imbalance. Other factors that predicted mortality in diabetics but not in nondiabetics were male gender and preoperative renal insufficiency. In several studies, survival of males, both diabetic and nondiabetic, has been found to be poorer than in a matched normal population.[24-27] In a study by Hiltunen et al,[24] the 4-year survival rate for Finnish diabetic men was 85% compared with 96% for diabetic women. In our study we were able to compare only 30-day outcome, as long-term data were not available, yet diabetic men seemed to have higher early mortality than men without diabetes or women with or without diabetes. Unfortunately, severity of preoperative renal insufficiency cannot be determined from Finnvasc data as all stages from moderately increased creatinine to end-stage renal disease with dialysis were clustered together. Our suggestion is that diabetics have more severe renal disease and that the proportion of dialysis patients among those with preoperative renal risk factor is higher in diabetics than in nondiabetics. Due to this, renal risk factor would be associated with early postoperative mortality in diabetics.

CONCLUSION

Diabetes is an independent risk factor for early postoperative myocardial ischemia, BK amputation, and wound infection. Early diagnosis of CLI as a potential reason for diabetic foot problems is of outmost importance. In diabetics, preoperative cardiac assessment is mandatory even if patient does not have diagnosed coronary artery disease or classical symptoms. This should be remembered also in the case of urgent operation, when preoperative time for assessment can be limited.

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IMPACT OF ENDOVASCULAR TREATMENT ON CLINICAL STATUS AND HEALTH-RELATED QUALITY OF LIFE

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ABSTRACT

Background and Aims: **Investigating the impact of percutaneous transluminal angioplasty (PTA) on clinical status and health related quality of life in patients with claudication and critical limb ischaemia (CLI).**

Material and Methods: **61 patients and 64 limbs underwent a primary PTA (30 claudication and 34 CLI cases). Clinical status was graded according to Ahn and Rutherford and ankle/brachial index (ABI). Quality of life was assessed using the Nottingham Health Profile (NHP) preoperatively, one month and one year after the procedure. Triplex scan evaluation of the treated arterial segment was carried out postoperatively and one year after the procedure.**

Results: **Claudication: 24/27 patients underwent one-year follow up, after which 20/24 had no claudication. In triplex evaluation 17 (63.0%) treated segments were open with 0–50% restenosis, 9 (33.3%) with 51–99% restenosis and one (3.7%) was occluded. CLI: 13/34 (38.2%) patients underwent one-year follow-up after which eight patients (61.5%) were asymptomatic and five (38.1%) had claudication. In triplex evaluation there was 0–50% restenosis in 6 (46.2%) segments treated with PTA and 51–99% restenosis in 7 (53.8%) segments. 21 (61.8%) patients did not conclude the one year follow up: 7 had died, 5 had undergone bypass surgery and 6 an amputation and 3 did not attend the follow-up up for unknown reasons. Quality of life: For CLI patients, improvement was observed in the domain of pain, which continued throughout the follow-up period. Among the claudicants, the domain of physical mobility was improved at one month's follow-up, but this effect disappeared during the following year and could not be seen at one the one- year follow-up.**

Conclusions: **Technical success and one-year results in claudication are good, and the rate of complications is low. However, although PTA resulted in an immediate improvement in the quality of life, this effect was not seen in the long term. In critical limb**

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ischemia there was a group of patients in whom PTA led to a significant benefit in terms of limb salvage and quality of life.

Key words: Intermittent claudication; critical limb ischaemia; percutaneous transluminal angioplasty; quality of life; claudication; vascular surgery

INTRODUCTION

Endovascular treatment of chronic lower limb ischemia is less invasive and usually achievable at the time of angiography. Patients with claudication often have smaller atherosclerotic manifestations than those with critical limb ischemia (CLI), and moderate lesions can often be treated with percutaneous transluminal angioplasty (PTA). In patients with CLI and widespread atherosclerotic lesions, endovascular treatment is rarely possible and bypass reconstruction is usually preferred. However, the risks of open surgery are unacceptable for some patients. In these cases, PTA may offer an alternative for avoiding amputation. The crucial question is, what the effectiveness and patency of PTA is in the long term. Does it prevent amputations in patients with critical limb ischemia or increase the quality of life for a claudicants?

The impact of PTA on the quality of life (QoL) of claudicants has been indefinite (1), and the QoL studies with CLI patients are based mainly on bypass surgery treatments (2). Moreover, the success of intervention has been described in terms of graft patency and limb salvage (3).

In this prospective, nonrandomized study, we analyse the haemodynamic results of PTA, and evaluate the quality of life of the patients before and after the PTA procedure.

MATERIAL AND METHODS

A total of 61 consecutive patients and 64 limbs underwent a primary PTA procedure in a teaching hospital of an academic institution during a period of 18 months. The study was approved by the local ethics committee, and written consent to participate was obtained in all cases. Data were collected prospectively. Clinical criteria for categories of chronic limb ischemia were outlined according to Ahn and Rutherford (4). The clinical grades I (claudication), II (ischemic rest pain) and III (tissue loss) account for the different natural histories of each group. Ankle/brachial index (ABI) was used as a noninvasive hemodynamic assessment together with triplex scan evaluation performed immediately and one year after the PTA procedure. Quality of life was assessed using the Nottingham Health Profile (NHP) developed by Hunt and McEwen (5), and the Finnish version was employed in this study (6). The NHP is a two-part instrument, and part I was used. The 38 yes/no items reflect the patient's degree of distress within the domains of pain, physical mobility, emotional reactions, energy, social isolation and sleep. The answer is given as a score between 0 and 100 describing the degree of harm in each item. The NHP questionnaire was filled out before the PTA procedure as well as one month and one year after the procedure.

The clinical characteristics of patients are summarized in Tables 1 and 2.

The data were statistically analysed using the SPSS software. Mean values of the variables between claudicants and CLI patients were compared using the independent samples t-test or the Mann-Whitney test. The means of the preoperative, 30-days follow-up and one-year follow-up values were compared using the dependent samples t-test or the Wilcoxon test and general linear models for repeated measures.

ENDOVASCULAR TECHNIQUE

All interventions were performed under local anaesthesia using the standardized technique. Access to the iliac lesions was obtained via an ipsilateral retrograde puncture of the common femoral artery and to the femoropopliteal and crural lesions via an ipsilateral antegrade puncture. The sheet was always used. Intravenous heparin (5000 units) was administered prior to the PTA. Technical success was defined as residual stenosis with less than 30% lumen reduction. Stents were used in 22 of the 25 iliac lesions, half of which were self-expandable nitinol and the remaining half balloon- expandable stainless steel stents. In 2 of 15 femoral lesions, nitinol stents were used due to unsatisfactory primary results with a balloon. All patients received aspirin (100 mg daily) after the procedure.

TABLE 1

Characteristics of the subjects treated with angioplasty for critical limb ischemia (61 cases; mean age ± SD: 71.8 ± 10.9 years).

Variable	n	%
Male	39	64
Female	22	36
Coronary artery disease	25	41
Diabetes mellitus	34	56
Hypertension	37	61
Smoking	16	26
Hyperlipidaemia	16	26
Renal insufficiency	3	5
Cerebrovascular disease	9	15
Chronic obstructive lung disease	7	11

TABLE 2

Characteristics of the limbs treated with angioplasty.

Variable	n (stent)	%
Indication for PTA		
Claudication	30	47
Ischemic rest pain	10	16
Ulcer / gangrene	24	37
The most distal artery treated		
Iliac artery	25 (22)	39
Superficial femoral artery	15 (2)	
Popliteal artery	13	39
Crural arteries	11	22

PTA: Percutaneus transluminal angioplasty

SONOGRAPHY

The vessels were examined after revascularization with Color Flow Duplex sonography. The site of the PTA and stent was located with colour and the grade of the residual stenosis was measured. In addition, the haemodynamic status was analysed with pulsed wave Doppler sonography, and the possible residual stenosis was estimated using the peak flow and the Doppler waveform. The examination was carried out by two independent radiologists who did not participate in the PTA procedures.

RESULTS

CLAUDICATION

Twenty-seven claudication patients and 30 limbs were treated, with a mean preoperative ABI of 0.63. The mean age of the claudication patients was 69.3 years (SD 10.7). One patient sustained a complication (1/27, 3.3%), stroke, the day of the PTA. All limbs underwent triplex-ultrasound after the PTA. 20/30 (66.7%) of the treated areas were open with 0–50% residual stenosis, and 10 limbs had residual stenosis of 51–99%. None of the sections treated were occluded. 26 patients underwent a 30-day clinical follow-up. One patient did not arrive at the 30-day control but did attend the one-year control with no claudication, the treated segment open with 0–50% restenosis and ABI 1.02 in the treated limb. At 30 days, 22/26 (84.6%) patients with a total of 27 treated limbs had no claudication, and 3/26 (11.5%) had claudication. The mean ABI in patients who underwent 30-day follow-up increased from the preoperative 0.63 to 0.84. 24 patients and 27 treated limbs underwent one-year follow-up, including a clinical control visit and triplex-ultrasound: 21/24 (87.5%) had no claudication, and 3/24 (12.5%) had claudication which had been present throughout the one-year follow-up period. Triplex ultrasound showed that 17/27 (63.0%) controlled sections were open with 0–50% restenosis, 9/27 (33.3%) were observed to have 51–99% restenosis, and 1/27 (3.7%) PTA segment was occluded. The mean ABI in these patients was 0.63 preoperatively and 0.85 at one year's follow-up. Three patients did not attend the control examination: one patient was in a very poor general condition and did not wish to attend the follow-up, and 2 patients did not come to the one-year control despite several calls, the reason for which remained unknown.

CRITICAL LIMB ISCHEMIA

Thirty-four patients (and 34 legs) with critical limb ischemia underwent PTA during the study period. The mean preoperative ABI of patients treated was 0.56, and the mean age of the CLI patients was 75.7 years (SD 10.1). The indications were ischemic rest pain for 10 (29.4%) and ulceration or gangrene (tissue loss) for 24 (70.6%) patients. Two patients (5.9%) sustained a complication postoperatively a groin haematoma which did not require intervention in either case. All patients underwent triplex-ultrasound one day after the PTA. 13/34 (38.2%) segments were open with residual stenosis of 0–50% in 20/34 (58.8%) there was residual stenosis 51–99%, and one of the treated sections occluded immediately. 27 of the 34 patients underwent 30-day clinical follow-up. At 30 days, 6/34 (18.6%) patients were asymptomatic and 9/34 (26.5%) had claudication, one patient (2.9%) rest pain and 11/34 (32.4%) patients an ulceration. Seven patients did not undergo 30-day follow-up for the following reasons: one patient underwent bypass reconstruction, two patients died, three patients had an amputation, and one patient did not attend despite several invitations. The mean ABI in patients who underwent 30-day follow-up increased from 0.54 to 0.67.

13 patients underwent one-year follow-up including a clinical control visit and triplex-ultrasound. None of them suffered from critical limb ischemia at that time: eight patients were asymptomatic and five had claudication. In one-year triplex control, six patients had restenosis of 0–50% in the PTA-treated arterial segment, and seven patients had 51–99% restenosis. No occlusions were observed. Among the 13 patients who underwent one-year follow-up, ABI had increased from the preoperative 0.56 to 0.86 at one year's follow-up. 21 patients did not undergo one-year follow-up: seven patients had died, six patients underwent an amputation, and bypass surgery was performed on five patients. Three patients did not observe the invitation to attend the control examination, one of whom was in institutional health care and in a very poor condition at the time.

PTA LEVEL

Results according to anatomic level of PTA are presented in Table 3.

QUALITY OF LIFE

Quality of life was measured preoperatively, at 30 days' follow-up and at one year's follow-up. There were only 14 claudicants and 7 CLI patients who answered the questions on all occasions. In Table 4 the means in each subgroup are compared to the mean of the population (value in the first column), and significant differences are found. The 36 different tests have not been combined; the results have been interpreted separately. The last three columns represent the significances of the pairwise comparisons in the general linear models for repeated measures, comparing the values at three different points in time. In the domains of energy and pain, claudicants seemed to improve their value after one month, but these changes were not quite statistically significant, and at one year's follow-up, the scores were significantly worse than at one month's follow-up. For both claudicants and CLI patients, the mean value for energy is even worse at one year's follow-up than preoperatively, but the difference is not statistically significant. For CLI patients, improvement was seen in the domain of pain, which continued at both follow-up points, and the difference was statistically significant between the one-year follow-up and the preoperative score. In the domain of sleep, there was significant

TABLE 3

One-year patency of PTA according to anatomy and extension of the lesion.

Claudication	Residual stenosis (%)				
	N	0–50	51–99	occluded	not controlled
Iliac artery	17	12	3	0	2
Femoropopliteal	13	5	6	1	1
Tibial arteries	0	0	0	0	0
Critical limb ischemia	Residual stenosis (%)				
	N orig	0–50	51–99	occluded	not controlled
Iliac artery	82	2	0	4	
Femoropopliteal	11	1	0	0	10
Tibial arteries	15	3	5	0	7

TABLE 4

The quality of life in patients who underwent PTA (F = Fontaine).

		Preoperatively (1st)				1 month (2nd)				1 year (3rd)				Differences between measurements in time: (P) for		
	Control[1]	Mean	(Std.D)	n	(P)[2]	Mean	(Std.D)	n	(P)[2]	Mean	(Std.D)	n	(P)[2]	1st vs 2nd	2nd vs 3rd	1st vs 3rd
Energy	17.30															
F II		25.14	(32.63)	21	(n.s.)	21.91	(29.13)	18	(n.s.)	33.67	(38.82)	23	(n.s.)	(n.s.)	(0.004)	(n.s.)
F III–IV		33.93	(31.41)	22	(0.022)	26.68	(28.93)	17	(n.s.)	42.76	(42.91)	11	(n.s.)	(n.s.)	(n.s.)	(n.s.)
Sleep	21.90															
F II		36.95	(31.39)	21	(0.040)	31.72	(32.24)	18	(n.s.)	26.13	(29.93)	23	(n.s.)	(n.s.)	(n.s.)	(0.010)
F III–IV		40.69	(35.67)	24	(0.017)	32.45	(32.82)	15	(n.s.)	18.37	(19.94)	11	(n.s.)	(n.s.)	(n.s.)	(0.015)
Pain	17.90															
F II		38.33	(24.25)	21	(0.001)	24.56	(28.55)	19	(n.s.)	33.08	(24.20)	22	(0.008)	(n.s.)	(0.006)	(n.s.)
F III–IV		42.43	(33.89)	24	(0.002)	26.11	(33.52)	16	(n.s.)	23.18	(17.54)	11	(n.s.)	(n.s.)	(n.s.)	(0.037)
Emotional reactions	11.30															
F II		17.01	(27.56)	21	(n.s.)	10.99	(18.56)	19	(n.s.)	12.18	(22.55)	22	(n.s.)	(n.s.)	(n.s.)	(n.s.)
F III–IV		21.08	(27.31)	25	(n.s.)	14.52	(25.83)	17	(n.s.)	10.50	(18.54)	11	(n.s.)	(n.s.)	(n.s.)	(n.s.)
Social isolation	17.40															
F II		7.99	(18.23)	22	(0.025)	10.07	(14.89)	19	(0.046)	9.71	(14.12)	22	(0.018)	(n.s.)	(n.s.)	(n.s.)
F III–IV		11.19	(14.21)	27	(0.032)	8.71	(11.33)	17	(0.006)	1.49	(4.94)	11	(0.000)	(n.s.)	(n.s.)	(n.s.)
Physical mobility	17.70															
F II		35.92	(27.60)	19	(0.010)	18.09	(21.02)	19	(n.s.)	27.09	(24.41)	23	(n.s.)	(0.007)	(0.005)	(n.s.)
F III–IV		41.68	(28.23)	26	(0.000)	28.74	(28.00)	16	(n.s.)	30.08	(27.23)	11	(n.s.)	(n.s.)	(n.s.)	(n.s.)

[1] mean in age matched control population
[2] P-value in testing difference between mean and control[1] value

improvement for claudicants at one month's follow-up, and it continued until the one-year follow-up was concluded. For CLI patients, the improvement was not so clear, but they also reported significantly improved values at one year's follow-up than preoperatively. Among claudicants, the domain of physical mobility was significantly better at the one-month point than preoperatively, but at the one-year follow-up, the improvement had nearly disappeared and the score was no longer significantly better than preoperatively.

DISCUSSION

The role of PTA in the treatment of limb-threatening ischaemia has increased significantly during the last five years. At the end of the last decade, the general opinion was that the PTA should not be considered as a primary treatment for CLI except in extraordinary circumstances (7). The effectiveness of PTA in the treatment in aortoiliac occlusive disease and claudication has been well established since the early 1990s (8,9). The enthusiasm towards PTA due to improvements in endovascular technology and expertise has led to suggestions that PTA should be the first choice for most of the patients requiring lower-extremity revascularization (10–12). In patients with claudication and relatively short lesions in arteries proximal to the popliteal artery, the clinical benefits of PTA compared to bypass surgery are clear: there is no need for general or spinal anaesthesia, the disadvantages of reconstructive surgery including surgical wounds are avoided, the hospital stay is shorter and the rates of complications and mortality are low. (12, 13). However, the role of PTA for CLI is still controversial. Furthermore, an aspect that is at least as important as technical success and patency for claudication patients is the change in the quality of life of these patients.

The technical success of PTA procedures is high and the clinical result of the treatment can be measured in an objective manner by noninvasive methods. In the current study, the technical success was 100%, and postoperative complications were rare. Only one patients sustained a serious complication, stroke, and he recovered well with no permanent symptoms. Furthermore, the clinical success for claudication patients was good: only 1 PTA segment was occluded at one-year follow-up and more than 80% of patients were free of claudication.

Patients with critical limb ischemia (CLI) differ significantly from those suffering from claudication. CLI-patients may have a widespread atherosclerotic disease and serious risks regarding open surgery. On the other hand, some CLI patients may be suitable for both endovascular and open reconstructive treatment. As a whole, the present study demonstrates the poor outcome of CLI patients with high mortality and morbidity rates. However, one third of the CLI patients survived with no critical ischemia at one-year follow up. Those patients with rest pain seem to gain more benefit, whereas the outcome was poorer in legs with tissue loss.

Proof of the efficacy of the procedure has been requested, as the current evidence regarding QoL following PTA is equivocal especially among claudicants (14, 15). Several generic quality of life instruments have recently been tested and used among vascular surgery patients. In this study, NHP was chosen, because at the time when the study was initiated, it was one of the few instruments that had been translated into Finnish and valuated and validated for the Finnish population (6). The NHP has been shown to be reliable among vascular surgery patients in earlier studies (2). Klevsgård et al. (2) demonstrated that the NHP was better than the Short-Form 36 Health Survey (SF-36) for patients with lower limb ischaemia with regard to pain and physical mobility and our experience is that the NHP was very effective in those domains.

Filling out the NHP questionnaire independently proved to be difficult or even impossible for many of our patients especially among the CLI-patients who are older and whose more serious illness causes varying levels of disability. Problems with reading or writing are reflected in the willingness to fill out a long questionnaire. Some of he NHP questions involving the domain of social isolation caused embarrassment to the patients and the results of the questionnaire in that domain are not reliable. Chronic neurological brain diseases such as dementia and Alzheimer's disease makes the evaluation of the quality of life impossible with any questionnaires. Because of these problems, we had to exclude improperly filled out forms, which has caused some selection in our results.

The responses in the domains of energy, sleep, pain and physical mobility were more reliable than those given with reference to emotional reactions and social isolation. Our assessment is that patients found it easier to answer these questions. Because there were only 11 patients with CLI at one-year follow-up who were able to answer the questions, the differences between the mean values did not reach statistical significance. In the domain of energy, an improvement could be seen in both groups, CLI and claudication, but this was statistically significant only for the claudicants. This improvement disappeared during the following year, and indeed the value worsened compared to the preoperative situation. The same phenomenon could be seen in the domain of pain for claudicants. One explanation might be that the disappearance of claudication pain improved the value at the one-month control but the patients forgot this benefit during the following year. The patients suffered from many other co-morbidities that affected the results in the domain of energy. In CLI patients, the scores in the domain of pain improved postoperatively and the improvement continued up to the one-year control. The improvement was statistically significant when the preoperative scores and the situation at one-year's follow-up were compared.

In the domain of physical mobility, the improvement for claudicants was clear and statistically significant up to the one-month follow-up, but again this improvement nearly disappeared during the following year. In the CLI group, there were no changes in the QoL value of mobility, which can be understood in that poor general health in CLI patients causes immobility along with limb ischemia and although leg salvage is achieved, patients stay relatively immobile.

The role of PTA in the treatment of CLI remains unclear. In the present data, the one-year outcome of CLI patients was relatively poor. Morbidity and mortality are low after endovascular procedures, but the risks and the rate of complications are high, including cardiac events and local morbidity (11, 12, 16). Therefore it is a significant finding that a subgroup of CLI patients gained a clear improvement which remained one year after PTA.

Claudication patients are generally believed to benefit from PTA. Although our one year clinical results and technical success were good, as almost 90% of the patients were free from claudication, the quality of life seemed to have deteriorated to the preoperative level with regard to the domains of pain and physical mobility. Whyman et al. (17) reported no correlation between improved ABI, walking distance and quality of life score at 6 months, except with regard to pain, among claudicants treated with angioplasty. Chetter et al. (1) similarly observed in their study that unilateral claudicants undergoing PTA on a solitary iliac lesion demonstrated the most marked QoL benefits and, 12 months post-PTA, reported a QoL approaching that of an age-matched population. In contrast, Klevsgård (2) reported that successful treatment of chronic limb ischaemia improved the quality of life for claudicants in their six-month follow up study.

Discrepancies between the technical success of

PTA, improvement in Fontaine classification and long-term improvement in the quality of life indicates that there are no reliable methods to analyse the effects of PTA-procedures in the treatment of claudication. Our study raises the question whether the treatment of claudication provides any long term improvement in quality of life.

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PREDICTORS FOR THE IMMEDIATE AND LONG-TERM OUTCOME OF A VASCULAR SURGICAL PROCEDURE

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ABSTRACT

Background and Aims: **The ability to predict post-operative mortality reliably will be of assistance in making decisions concerning the treatment of an individual patient. The aim of this study was to test the GAS score as a predictor of post-operative mortality in vascular surgical patients.**

Material and Methods: **A total of 157 consecutive patients who underwent an elective vascular surgical procedure were included in the study. The Cox proportional hazards model was used in analyzing the importance of various preoperative risk factors for the postoperative outcome. ASA and GAS were tested in predicting the short and long-term outcome. On the basis of the GAS cut-off value 77, patients were selected into low-risk (GAS low: GAS < 77) and high-risk (GAS high: GAS > = 77) groups, and the examined risk factors were analyzed to determine which of them had predictive value for the prognosis.**

Results: **None of the patients in the GAS low group died, and mortality in the GAS high group was 4.8% (p = 0.03) at 30 days' follow-up. The 12-month survival rates were 98.6% and 78.6% (p = 0.0001), respectively, with the respective 5-year survival rates of 76.7% and 44.0% (p = 0.0001). The only independent risk factor for 30-day mortality was the renal risk factor (OR 20.2). The combination of all three GAS variables (chronic renal failure, cardiac disease and cerebrovascular disease), excluding age, was associated with a 100% two-year mortality.**

Conclusions: **Mortality is low for patients with GAS < 77. For the high-risk patients (GAS > = 77), due to its low predictive value for death, GAS yields limited value in clinical practice. In cases of patients with all three risk factors (renal, cardiac and cerebrovascular), vascular surgery should be considered very carefully.**

Key words: Vascular surgery; risk factors; mortality; outcome; perioperative risk; assessment; survival

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INTRODUCTION

A number of rating systems have been developed to predict operative risks and postoperative mortality in surgical patients. Because of their complexity, there has been a need to find a model for assessing operative risk that is easy to both calculate and use. Samy et al. (1,2) derived and validated a simple scale, the Glasgow Aneurysm Score (GAS), for risk stratification of patients undergoing elective and emergency open repair of an abdominal aortic aneurysm (AAA). In the study by Biancari et al. (3), GAS proved to be a good predictor of mortality after elective open repair of an AAA, in addition to its simplicity and accuracy. Most of the related studies have evaluated the value of risk scores in predicting operative mortality and morbidity. However, long-term outcome is also important when surgical procedures are planned for the patients. In the case of poor long-term mortality, the patient may not gain the benefit from the procedure and the operation may even cause more harm than non-surgical treatment. These facts raised the question whether the operative risks and long-term mortality of vascular surgery patients could generally be predicted with risk scoring methods. The aim of the current study was to evaluate the importance of different risk factors for the mortality of vascular patients, in addition to assessing the usefulness of the GAS and ASA classifications in predicting the immediate postoperative and long-term mortality of patients undergoing vascular surgery.

MATERIAL AND METHODS

A total of 157 consecutive patients who underwent an elective vascular surgical procedure in a teaching hospital between 9 April 2002 and 9 April 2003 were included in the study. The study was approved by the local ethics committee, and written consent to participate was obtained in all cases.

Data was collected prospectively. The data recorded comprised a patient history from case reports, anamnesis and physical examination as well as electrocardiography (ECG), chest radiography and basic laboratory testing including serum creatinine and haemoglobin levels. The preoperative examination and data collection were performed by a vascular surgeon or vascular surgical fellow, and the ASA (American Society of Anesthesiologists) score was determined by an anaesthetist.

Patients were divided into three groups according to the indication for surgery: carotid procedures for cerebrovascular circulation, chronic limb ischaemia and abdominal aortic aneurysm.

The Glasgow Aneurysm Score (GAS) was calculated using the formula: risk score = age in years + 7 (for myocardial disease) + 10 (for cerebrovascular disease) + 14 (for renal disease) (1, 2). Myocardial disease refers to a previously documented myocardial infarction and/or ongoing angina pectoris. Cerebrovascular disease refers to all grades of stroke including transient ischaemic attack (TIA). Renal disease refers to a history of chronic and acute renal failure, and/or a serum level of creatinine greater than 140 µmol/l at the time of surgery. Patients were divided into two GAS groups based on the study by Hirzalla et al. (4): GAS <77 (GAS low) and GAS>=77 (GAS high).

A postoperative renal complication was defined as an increase in the serum concentration of creatinine or urea that required medical treatment or dialysis. A postoperative cardiac complication was defined as a myocardial infarction (ECG changes or increased serum troponin level) or death due to cardiac causes, as well as postoperative cerebrovascular complications such as a TIA or stroke. Long-term mortality data up to 5 years postoperatively were obtained from the cause of death registry of Statistics Finland. No patients were lost from the follow-up.

The data were statistically analysed using the SPSS 13.0 software. Data are expressed as mean value and standard deviation. The Chi-Square test, logistic regression as well as the Cox proportional hazards model and the Kaplan-Meier Survival Analysis were used in data analysis.

RESULTS

Demographic data of the patients are presented in Table 1. The most common indication for the procedure was chronic limb ischaemia (60.5%, 95/157), followed by carotid disease (26.1%, 41/157) and abdominal aortic aneurysm (13.4%, 21/157).

The 30-day mortality rate was 2.5% (4/157). The incidence of postoperative complications is presented in Table 2. The only independent risk factor for 30-day mortality was the renal risk factor (OR 20.2) (Table 3A). None of the patients in the GAS low group died, and the mortality rate in the GAS high group was 4.8% ($p = 0.03$).

During the 5 years following the procedure, 40.8% (64/157) of the patients died. In the Cox proportional hazards model, independent predictors for long-term mortality included the renal risk factor (OR 3.9), the cardiac risk factor (OR 2.3), age (OR 1.04/year) and

TABLE 1

The characteristics of the patients

	Patients (n = 157)
Mean age / SD	69.9 / 9.3
Male:female (%)	66 : 34
Hyperlipidemia[1]	36.1
Hypertension[2]	43.7
Cardiac[3]	25.9
Cerebrovascular[4]	37.3
Pulmonal[5]	18.4
Renal[6]	6.9
Smoking[7]	36.1
Diabetes	27.2
GAS < 77 / > = 77	73 / 84
Mean GAS / SD	75.7 / 11.6
ASA 1 / 2 / 3 / 4	0 / 10 / 109 / 37

1 Serum concentration of cholesterol > 5.0 mmol/L or LDL > 3.0 mmol/L or triglycerides > 2.0 mmol/L
2 Medication for hypertension or arterial pressure > 145/85 mm Hg
3 NYHA III–IV
4 History of stroke or transient ischaemic attacks
5 Asthma or chronic obstructive pulmonary disease
6 History of chronic and acute renal failure, or a serum level of urea over 20 mmol/L or serum level of creatine over 140 µmol/L
7 Current smoker
8 Glasgow Aneurysm Scale
9 American Society of Anesthesiologists

TABLE 2

Complications of the patients during 30-day follow up. The number of complications leading to death is marked in parentheses together with the main indication for the operation.

Complication	Patients (n = 157)
Cardiac ischaemia	6 (2 deaths, leg ischaemia)
Acute renal failure	4
Acute graft occlusion	8
Disrupted laparotomy wound	2
Respiratory complication	8 (1 death, leg ischaemia)
Cerebrovascular complication	5
Superficial wound infection	15
Deep wound infection	2
Bowel ischaemia	4 (1 death, AAA)
Postoperative haemorrhage	9
Reversible nerve damage	6
G-I bleeding	1

procedure type (carotid surgery as a reference category: OR for an infrainguinal procedure 3.5 and for infrarenal aorta 3.3) (Table 3B). 12-month survival for the patients in the GAS low and GAS high groups was 98.6% and 78.6%, respectively ($p<0.0001$), the respective 5-year figures being 76.7% and 44.0% ($p=0.0001$). All 4 patients with renal disease, cardiac disease and cerebrovascular disease died within 2 years of the procedure. The Kaplan-Meier survival rates for patients according to the renal risk factor, the ASA classification and GAS are presented in Figure 1.

DISCUSSION

To ensure appropriate use of health care resources and avoid futile attempts at intervention in patients with high risk, the role of judicious patient selection is essential. On the other hand, the intuition of an experienced surgeon is generally based on quite obvious clinical symptoms. A number of scoring systems have been developed to predict outcome for patients and to assist in the decision-making in a more objective way, therefore justifying the procedure. The Physiological and Operative Severity Score for the enumeration of mortality and morbidity (POSSUM) (5, 6) is widely used among surgeons and can surely be considered a standard method, but its suitability for vascular surgical procedures (V-POSSUM), especially aortic aneurysm surgery (RAAA-POSSUM), has been doubted (7, 8). Furthermore, the POSSUM score was originally designed to support comparative audit and has not been recommended for outcome prediction. Moreover, it is relatively difficult to use in daily practice.

In the present study, the GAS cut-off value was determined at 77 according to Hirzalla et al. (4), dividing the patients into low and high-risk groups. A risk score of less than 77 predicted a fairly low mor-

TABLE 3A

Multivariate analysis of the risk factors for 30-day postoperative mortality. Dependent factor: 30-day mortality. Independent factors: Age, sex, operation type (carotid artery, infrarenal aorta, infrainguinal arteries); and preoperative risk factors: cardiac, renal, cerebrovascular, diabetes

FACTOR	OR	95% CI	P
Aortic surgery *(compared to carotid surgery)	na	na	na
Infrainguinal surgery* (compared to carotid surgery)	na	na	na
Age per 10 years	3.1	0.8–11.9	0.09
Cardiac risk	0.8	0.1–5.1	0.8
Renal risk	20.3	3.1–133	0.002
Cerebrovascular risk	2.1	0.3–15	0.4
Diabetes	0.8	0.1–6.5	0.7
Sex (male vs. female)	0.2	0.02–1.8	0.1

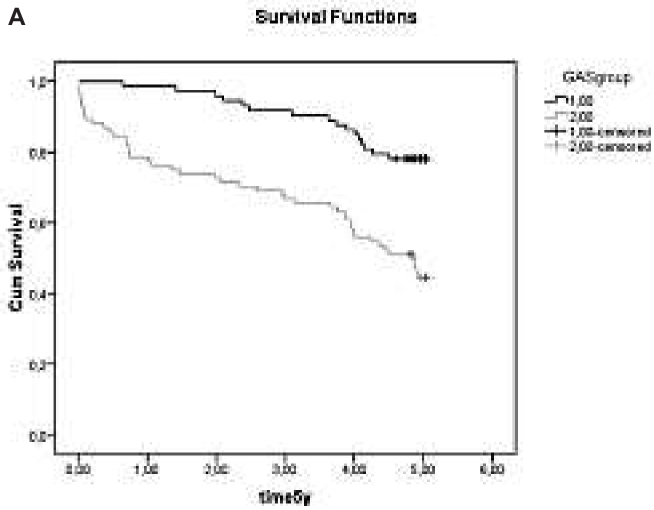
na = not applicable
* no values because 30-day mortality for carotid surgery was 0%

TABLE 3B

Cox proportional hazards model for long-term mortality after a vascular surgical procedure. Dependent factor: Mortality during 5 years after the procedure. Independent factors: Age, sex, operation anatomy (carotid artery, infrarenal aorta, infrainguinal arteries) and preoperative risk factors: cardiac, renal, cerebrovascular, diabetes

FACTOR	OR	95% CI	P
Aortic surgery (compared to carotid surgery)	3.3	1.2–9.6	0.004
Age per 1 years	1.04	1.01–1.1	0.02
Infrainguinal surgery (compared to carotid surgery)	3.5	1.4–8.8	0.007
Cardiac risk	2.3	1.3–3.8	0.002
Renal risk	3.9	1.7–9.0	0.002
Cerebrovascular risk	1.0	0.6–1.9	0.9
Diabetes	0.7	0.6–2.0	0.7
Sex (male vs. female)	0.6	0.3–1.2	0.1

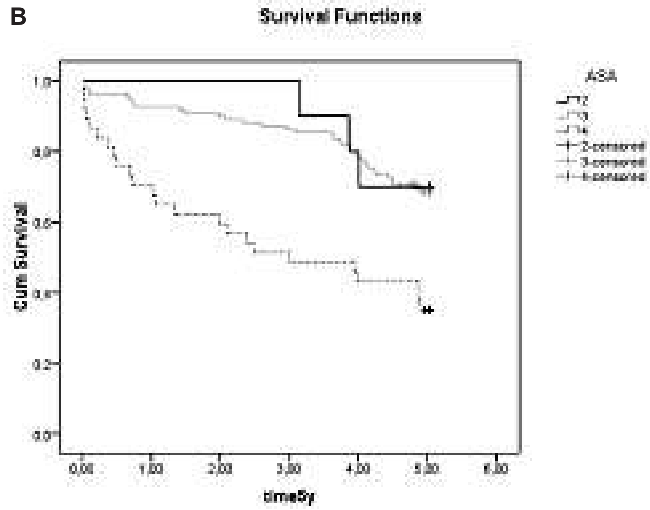
A



Patients at risk

GAS low	73	72	70	67	63	45
GAS high	84	66	61	56	47	31

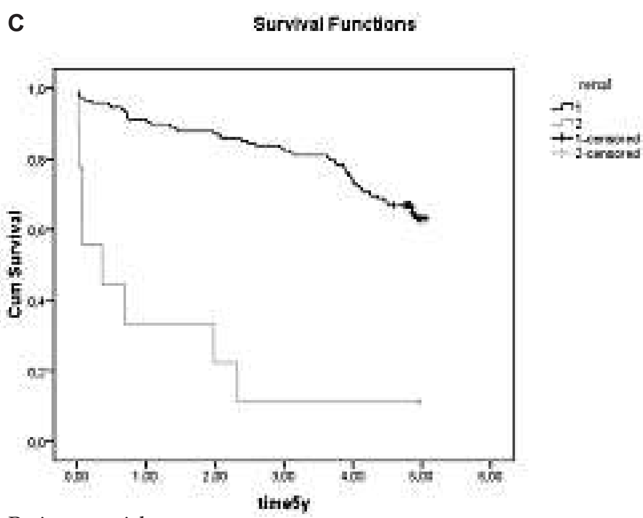
B



Patients at risk

ASA2	10	9	9	9	7	5
ASA3	110	101	98	93	84	57
ASA4	37	26	22	18	16	8

C



Patients at risk

Renal no	146	135	129	122	109	76
Renal yes	11	3	2	1	1	0

Fig. 1. Kaplan-Meier 5-year survival in low-risk and high-risk patients according the GAS classification (A) (1 = GSA low; 2 = GAS high), according to the ASA classification (B) and in patients with or without renal insufficiency (C) (Cut-off value for serum creatinine 140).

tality after procedures, while a risk score of higher than or equal to 77 was clearly associated with a higher mortality. However, the use of this method in clinical practice is limited. GAS has a good predictive value for patients who survive, but it is not as accurate in attempting to identify those patients who do not survive the operation or whose life expectancy after the procedure is limited.

Multivariate analysis of short-term mortality demonstrated that although renal insufficiency is a significant risk factor, diabetes alone without renal complications does not significantly increase the incidence of short-term mortality. With regard to long-term mortality in our study with five years' follow-up, renal insufficiency alone was connected with high mortality: none of these patients survived the follow-up period of five years. Cardiac disease appeared to be a strong risk factor in addition to renal insufficiency and age. The combination of all three GAS variables, with the exception of age, yielded an extremely high mortality rate: all of these patients died within two years' follow-up. Although the number of these patients was low – only four – the message is clear that these patients are at an extremely high risk after vascular surgery. What was interesting was that the survival rate for ASA 2 and ASA 3 patients was almost the same, being significantly better than among the ASA 4 patients. Because the number of ASA 2 patients was only 10, however, any strong conclusions cannot be made.

When comparing different types of surgical procedures, the group of carotid endarterectomy (CEA) patients seemed to manage better during a five-year follow-up than the groups of infrarenal aortic and infrainguinal patients, although carotid patients were significantly older than those included in other groups. In addition, GAS was higher for carotid patients due to the high age and to cerebrovascular disease of which nearly all of them suffered. However, the carotid patients had a lower incidence of cardiac and renal disease. Furthermore, although they had cerebrovascular disease, this risk decreased when the carotid stenosis was treated surgically. Therefore, the CEA risk assessment differs from the risk assessment for the other groups, and the importance of cerebrovascular disease should be considered in a different light for these patients.

Our study showed that GAS has predictive value for the prognosis after vascular surgical procedures, because the survival from infrarenal aortic and infrainguinal procedures was similar, and there is a need to perform external validation of GAS in vascular surgery procedures. Our estimation is that GAS is highly valid for the high-risk group even at the selected cut-off GAS score of 77 and that the individual high-risk patient requires special attention. Thereafter, GAS has good negative predictive value for vascular surgery patients. The observations are in line with other studies concerning AAA surgery (4, 9)

In vascular surgery, mortality is not an outcome measure except in aneurysm surgery, where the aim of the surgery is to avoid aneurysm rupture and death. In the treatment of critical limb ischaemia, the aim is to prevent amputation and thus maintain the patient's mobility and independence. In carotid surgery, the reasons for operating are to prevent stroke and death due to stroke. Surgery should be performed despite high risks if the patient's life expectancy is more than one year. If the life expectancy is very short, however, an operation causes unacceptable individual suffering for all patients. The aim of this kind of study is to help us distinguish patients at an extremely high risk. The number of patients included in the current investigation is too low to make any far-reaching conclusions, but some of the findings may be useful in evaluating individual patients in everyday clinical work.

CONCLUSION

Mortality is low among patients with GAS < 77. However, for the high-risk patients (GAS > = 77), due to its low predictive value for death, GAS yields limited value in clinical practice. In cases of patients with all three risk factors (renal, cardiac and cerebrovascular), vascular surgery should be considered very carefully.

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