LOWER LIMB ISCHEMIA IN WOMEN

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The last three decades in limb salvage surgery we discovered what we could do. Now it is time to learn what we should do.

John Porter, Professor of Surgery (1938-2001)
Oregon, United States

To Johan, Jakob and Josefine

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ABSTRACT

Arteriosclerosis is a general disease affecting different parts of the arterial system. In coronary heart disease (CHD) women have different risk factors, symptoms, indication for treatment, interpretation of diagnostic data and outcome than men. The overall aim of this thesis was to test the hypothesis that similar gender differences exist in patients with symptomatic arteriosclerosis in the arteries of the lower limb (LLI) and to investigate the magnitude of the problem.

***The Stockholm Study*.** The number of procedures performed, development over time, survival and amputation rates in women and men were investigated in a large epidemiological study of all patients treated with vascular interventions for lower limb ischemia (LLI) in the county of Stockholm in 1970-1994 (8660 patients, 12200 interventions).

An increase from 18 vascular interventions to 786 / million inhabitants and in the proportion of women from 34% in 1970 to 48% in 1994 was shown. Mean age increased from 63 to 71 years. Women were older than men (71 years vs 66, $p<0.001$). The localisation of lesions treated for chronic LLI was similarly distributed between women and men. Women had poorer survival than men. In a Cox regression model, increasing age, later calendar years and being a man were risk factors for poorer survival. In a multivariate analysis of the risk for amputation, age and calendar year were important risk factors, not gender.

Our results confirmed the clinical observation of an increasing proportion of women and elderly, possibly related to an increasing prevalence, better knowledge about LLI among referring doctors, improved technique and wider indication for treatment, especially in elderly. The similar or better results after intervention in women could be explained by the generally better survival in women in the population as well as a restrictive attitude towards treating women compared to men.

Women treated for critical ischemia. Specific gender differences in preoperative conditions, localisation of treated lesions, complications and long-term outcome was retrospectively investigated in patients treated for chronic critical limb ischemia at the Karolinska Hospital (KH) in 1993-1994 (n=234 patients).

Women were older than men (74 vs 68 years), smoking and diabetes was less frequent among women (smokers: 63 % vs 82%, $p=0.005$; diabetes: 22% vs 43%, $p=0.0004$). Other preoperative conditions were not worse in women. Women were more commonly treated with suprainguinal interventions than men (44% versus 19%). Outcome was similar for women and men.

The greatest disadvantage for women is their high mean age. The later onset for women could depend on biological differences combined with a different distribution of risk factors than in men. The different localisation of treated lesions can be related to age and anatomical differences. The similarities in outcome despite different preoperative conditions indicate that diabetic women with severe LLI are less frequently treated, alternatively men with high risk are offered interventions more generously.

Reproductive History. In order to evaluate the reproductive history in women with LLI compared with women in the population, 173 women treated for LLI in 1994-1996 at KH and 348 women living in the hospital catchment area were sent a validated questionnaire.

Age at menopause and menarche, pregnancies, hysterectomy and hormone replacement therapy were similar between women treated for LLI and women in the population. More references had used oral contraceptives than patients (53% vs 16%, $p<0.001$).

Women with LLI do not have a different reproductive history than women in the population, contradictory to women with CHD. The influence on the development of arteriosclerotic disease by other risk factors could be more important in LLI patients. Maybe oestrogen levels are less important for the progression of arteriosclerotic disease in other peripheral arteries compared to coronary and carotid arteries.

Conclusion

The number of vascular interventions, especially in women, have probably increased further after the observed period, and the increase can be expected to continue. Biological and anatomical differences can probably explain several of the found differences between the sexes, such as localisation of treated lesions and age. The similar outcome between women and men indicates that we should continue to focus on established risk factors in our preoperative evaluation, rather than gender or reproductive history in women.

Key words: lower limb ischemia, vascular surgery, women, gender outcome, reproductive history, menopause

ABBREVIATIONS

ABPI	Ankle Brachial Pressure Index
AIOD	Aortoiliac Occlusive Disease
ANOVA	Analysis of Variance
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Intermittent Claudication
CLI	Chronic Critical Limb Ischemia
HRT	Hormone Replacement Therapy
KH	Karolinska Hospital
LDL	Low density lipid protein
LLI	Lower limb ischemia
MI	Myocardial infarction
NBHW	National Board of Health and Welfare
PTA	Percutaneous transluminal angioplasty
SMR	Standard Mortality Ratio
SOE	Salpingoophorectomy
SWEDVASC	The Vascular Registry in Sweden
TG	Triglyceride

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to by their Roman numerals as indicated below:

I **Gender differences in vascular interventions for lower limb ischemia**
Hultgren R, Olofsson P, Wahlberg E
European Journal of Vascular and Endovascular Surgery 2001; 21, 22-27

II **Sex related Differences in Outcome after Vascular Interventions for Lower Limb Ischemia**
Hultgren R, Olofsson P, Wahlberg E.
Journal of Vascular Surgery 2002 ; 35: 510-6

III **Gender differences in patients treated for critical limb ischemia**
Hultgren R, Olofsson P, Wahlberg E
Submitted

IV **Reproductive history in women with lower limb ischemia**
Hultgren R, Olofsson P, Wahlberg E
Angiology , in press

INTRODUCTION AND BACKGROUND

Introduction

Arteriosclerosis is a general disease affecting different parts of the arterial system.

The three most common clinical manifestations are coronary heart disease (CHD), stroke and arteriosclerosis in the arteries of the lower limb. Extensive efforts to clarify possible gender differences in patients suffering from CHD have been made during the last decades. Apart from the interest in gender differences, the scientific community has tried to explain the relationship between oestrogen and the development and progression of CHD.

It is tempting to assume that specific conditions described for women with CHD are valid also for women with lower limb ischemia (LLI), but this needs to be verified.

The majority of patients treated for LLI with vascular surgery were male in the past. A clinical impression has been that women constitute a growing proportion of patients treated for LLI. The present knowledge about relevant gender differences in patients treated for LLI is poor.

A better knowledge of specific conditions in women with LLI can be of great potential importance to prevent disability and limb loss.

Arteriosclerosis

Arteriosclerosis is a process occurring in the media and intimal layer of large and medium sized arteries. It is characterised by an accumulation of cells (macrophages and monocytes), matrix fibres and lipids, resulting in a plaque narrowing the lumen diameter and causing obstruction of blood flow. The process usually occurs in bifurcations or bends due to hemodynamic variations. The arteriosclerotic plaque can rupture towards the lumen causing ulceration, embolisation and thrombus formation due to interactions with platelets and coagulation factors in the blood and vessel wall.

Arteries are more (coronary arteries, internal carotid artery, abdominal aorta, arteries in the lower limb) or less (thoracic aorta, common carotid artery and arteries of the upper limb) prone to develop arteriosclerotic plaques. The reason for this difference is not completely understood. The higher susceptibility for disease in the coronary arteries, internal carotid artery, abdominal aorta and arteries in the lower limb is reflected in the high incidence of angina or myocardial infarction, stroke and LLI in the population.

Unfortunately many patients suffer from multiple manifestations of arteriosclerosis. In the "PARTNERS" program in the United States; 55% of patients with LLI also have symptomatic cardiovascular or cerebrovascular disease and 40 % of patients with symptomatic cardiovascular or cerebrovascular disease have asymptomatic or symptomatic LLI. [1]

Risk factors for development of arteriosclerosis

Age

The prevalence of all manifestations of arteriosclerotic disease is related to increasing age. A decrease in the elastic properties, i.e. distensibility of the aorta and carotid artery with advancing age has been shown in women and men. [2] This is a natural physiological phenomenon, but is accelerated when risk factors such

as smoking are present. The arterial distensibility is also influenced by sex hormones. The femoral artery is however not influenced to the same extent as the aorta and carotid artery. [2] Another factor influenced by sex hormones and age is disturbances in the microcirculation. One example is an enhanced endothelial permeability allowing penetration of macromolecules, including lipoproteins and albumin, into the media layer. [3] Both oestrogen and testosterone have been shown to maintain the integrity of the wall structure. In men, the increase in arterial stiffness is found earlier than in women, but after menopause the process develops in similar ways in women and men.[2] Women suffering from arteriosclerotic disease are generally older than men (3-10 years). The reasons for this difference are still not completely understood.

Diabetes

Among patients treated for LLI, the proportion of diabetic patients varies between 24% and 65%. [4-8] The risk of development of LLI is 3-5 times higher in diabetic compared to non-diabetic patients and diabetes is probably a more significant risk factor in women than in men. [9, 10] Early menopause, the presence of the metabolic syndrome, hypertension and a negative lipid profile are common in diabetic women and contribute to their increased risk of CHD and LLI compared to non-diabetic women. [11] Diabetes is not only considered to be an independent risk factor for development and progression of disease, but it might also influence results after treatment of both MI and LLI negatively. [4, 12-14] A matching of patients for this factor in outcome investigations can minimise the risk for confounding.

Smoking

Smoking strongly affects the development of arteriosclerosis. [15-17] The effect is multi-factorial. Examples are stimulation of the inflammatory process in the vessel wall, the lowering of menopausal age and the elevation of fibrinogen and LDL levels. [15, 17-21] Smoking also affects the arterial wall differently in men and pre-menopausal women. The intima media thickness (IMT) in the carotid and femoral artery is increased in male smokers compared with non-smokers, a difference not found in pre-menopausal women. [21, 22] Sonesson et al found an increase in the arterial stiffness of the aorta in female smokers compared to non-smokers, a difference not found in men. “Menopausal state” was not defined in that study (median age 51 years, range 43-61), and this could have influenced the result. [16] In the Edinburgh and PARTNERS studies, smoking was more common in LLI than CHD patients. [1, 17] It is possible that peripheral arteries are more susceptible for the deleterious effects of smoking compared to coronary arteries.

Hyperlipidemia

Elevated total cholesterol, low density lipoprotein (LDL) and triglycerids (TG) have been identified as risk factors for the development of CHD, carotid arteriosclerosis and LLI. [9, 22-24] Few investigations have specifically studied the association between lipid levels and LLI in women. This may be explained by methodological difficulties due to the influence of physiological fluctuations during the menstrual cycle, the use of oral contraceptives and hormone replacement therapy (HRT). Endogenous changes in lipid levels also occur at the onset of menopause. Increased LDL and TG levels and decreasing HDL levels, could be

major contributing factors for the rapid progression of arteriosclerotic disease after menopause.

Reproductive history

It is the later onset of CHD in women compared to men that has initiated the hypothesis of a protective effect by endogenous oestrogen against arteriosclerosis in the pre-menopausal woman. Positive effects of oestrogen have been described in humans, animals and in vitro models. Examples are nitric oxide mediated vasodilatation, lowering of Lp (a), stimulation of angiogenesis, decreased expression of VCAM (vascular cell adhesion molecule) and ICAM (intracellular adhesion molecule) and lowering of LDL cholesterol. [25-33] Altogether most investigations analysing oestrogen show convincing beneficial effects against the development and progression of arteriosclerosis. It has however been very difficult to show similar beneficial effects by exogenous oestrogen in clinical trials, especially in women with CHD. [34-36]

If oestrogen is a "protector", low endogenous oestrogen levels throughout life would hypothetically increase the risk of developing arteriosclerotic disease. It has however been difficult to investigate if differences in the reproductive history influence this risk. There are some obvious methodological difficulties, for example the long time passing from the possibly disturbed oestrogen level to the actual onset of the disease. The only reproductive factor that has been shown to influence the risk of CHD with an acceptable level of scientific evidence is the age at which menopause occurs. Premature menopause (< 44 years), natural or surgical, increases this risk and possibly also the risk of plaque progression in the carotid artery. [37-43] In women with aortoiliac occlusive disease (AIOD), the influence of premature menopause was investigated in the 1970s. The relationship found between premature menopause and the progression of the disease appeared to be weak. [44, 45] Age at menarche does not influence the risk of CHD.[46, 47]
Multiparity (> 3 pregnancies) may increase the risk of development of CHD and carotid plaques. [41, 48, 49]

Contradictory results have been reported concerning the risk associated with the use of oral contraceptives. It may be related to the different "generations" of oral contraceptives. For second or third generation pills (lower oestrogen doses) the risk of acute myocardial infarction (MI) in non-smoking women is very low or non-existent. [50-54] The possible protective effect of HRT on cardiovascular morbidity and mortality is one of the most important factors to consider from the point of view of health economics. This was suggested in North American observational studies from the 1990s, but recent trials found an increased risk of cardiovascular events the first year of treatment compared to placebo.[34-36] Therefore, the American Heart Association does not recommend HRT as a primary or secondary prevention of CHD.[55]

Subgroup analysis of LLI in one of these trials (HERS), failed to show a beneficial effect on the progression of the disease by HRT. [56] The opposite was reported in the Rotterdam and Rancho Bernardo studies- a better ankle-brachial pressure index was found in women treated with HRT than untreated women. [57, 58] Both a positive and a negative effect on stroke incidence and carotid plaque progression by HRT has been reported. [59-62]

If normal oestrogen levels throughout life protects women against development or progression of LLI, treatment of lower oestrogen levels, for example after surgically induced premature menopause, could theoretically prevent disease. On the other hand, if oestrogen

levels do not influence the development of LLI, this can be interpreted as if coronary and peripheral arteries react differently in this respect.

Lower limb ischemia

Definitions

An impaired arterial blood flow to the lower limb due to arteriosclerotic lesions is called lower limb ischemia (LLI), peripheral arterial occlusive disease (PAOD) or peripheral arterial disease (PAD). The clinical manifestations of symptomatic chronic LLI are *intermittent claudication* (IC) and chronic *critical limb ischemia* (CLI). The classification by Fontaine from 1954 is still used. Table 1. Others have developed new tools for classification of these patients mainly for scientific purposes, such as the TransAtlantic Inter-Society Consensus document (TASC).[63] A patient suffering from IC experiences localised pain in the leg, always associated with exercise, that typically disappears after some minutes of rest. A patient with CLI describes extremely short walking distances and a severe pain in the fore foot in supine position, called *ischemic rest pain.* Table 1. The more severe manifestations of CLI, *non-healing ulcers* or *gangrene*, are typically localised in the toes, forefoot or ankle, and are more common in diabetic than non-diabetic patients. [64]

The preliminary diagnosis is based on the patient's medical history and a clinical examination, including comparison of the systolic blood pressure measured at the ankle and the arm. The *ankle-brachial pressure index (ABPI)* is calculated to compensate for variations in blood pressure. A decreased ABPI (<0.8 or <0.9) in an asymptomatic patient is defined as *asymptomatic PAOD.* [58, 65, 66]

The localisation and distribution of the arterial lesion vary extensively and have implications for the indication for treatment and results. In s*uprainguinal disease*, the arterial lesion is located above and in *infrainguinal disease* below the inguinal ligament. Some differences in the characteristics between the two groups are listed below, Figure 1.[13, 44, 64, 67-76] Many patients have a combination called "multilevel" disease. Patients who at the primary evaluation are candidates for intervention, will be referred for duplex sonography or angiography. These examinations will reveal the presence and localisation of significant stenosis or occlusions, the length of the lesion and in- and outflow

Table 1. Classification of LLI by Fontaine.

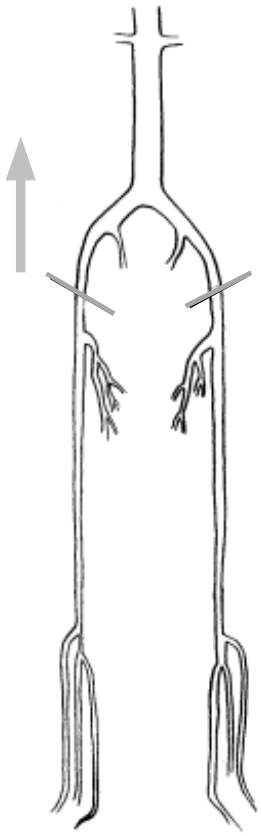
I	asymtomatic arteriopathy
II	exercise induced ischemia a) intermittent claudication >100 m b) intermittent claudication <100 m
III	ischemia related pain at rest a) ankle pressure >50 mmHg b) ankle pressure <50 mmHg
IV	trophic ulcers and gangrene a) limited gangrene b) extensive gangrene

conditions. These anatomical conditions influence the decision regarding which interventional therapy to recommend. Table 2. Chronic lower limb ischemia can be treated with *vascular reconstruction* or *endovascular intervention.* In the following text, the term "*vascular intervention"* refers to both types of treatment. A limited localised arteriosclerotic plaque can be extracted locally, so called thrombendarterectomy. Often the arterial tree is more generally affected, necessitating a bypass procedure using a graft.

For infrainguinal reconstruction, autologous vein grafts provide superior short and long term results compared to other materials. Synthetic grafts (PTFE or Dacron) can be used in suprainguinal reconstructions and occasionally in femoropopliteal reconstructions above the knee. *Endovascular intervention* or *percutaneous transluminal angioplasty* (PTA*)* is performed by a radiologist or vascular surgeon, using a "balloon catheter" to restore the lumen diameter by dilatation of the lesion. An arterial embolus is usually extracted with a specially designed balloon catheter (Fogarthy catheter), an *embolectomy.* A *major amputation* is defined as an amputation above or proximal to the tarso-metatarsal joint. Primary amputation is performed without attempting vascular intervention and a secondary amputation is performed after vascular intervention. Occasionally "minor amputations" are presented in reports.

Figure 1. *Suprainguinal disease refers to lesions located in the aorta and iliac arteries. Infrainguinal disease refers to lesions located in the femoral, popliteal or calf arteries. The knee joint divides the popliteal artery into above- and below knee segments. Infrainguinal reconstructions to calf arteries are often referred to as distal reconstructions.*

Suprainguinal disease
Large lumen diameter
High blood flow
Low peripheral resistence
Short distances for by pass
Mean age in treated 55-65 years
Claudication >critical ischemia
Women 30-40%
Smoking 70-100%
Diabetes 5-26 %
Amputation rate 1 year 0-10%
Mortality rate 1 year 4-10%



Infrainguinal disease
Small lumen diameter
Low blood flow
High peripheral resistance
Long distances for bypass
Mean age in treated 65-75 years
Critical ischemia>claudication
Women 40-60%
Smoking < 80%
Diabetes 24-65 %
Amputation rate 1 year 4-30%
Mortality rate 1 year 12-26%

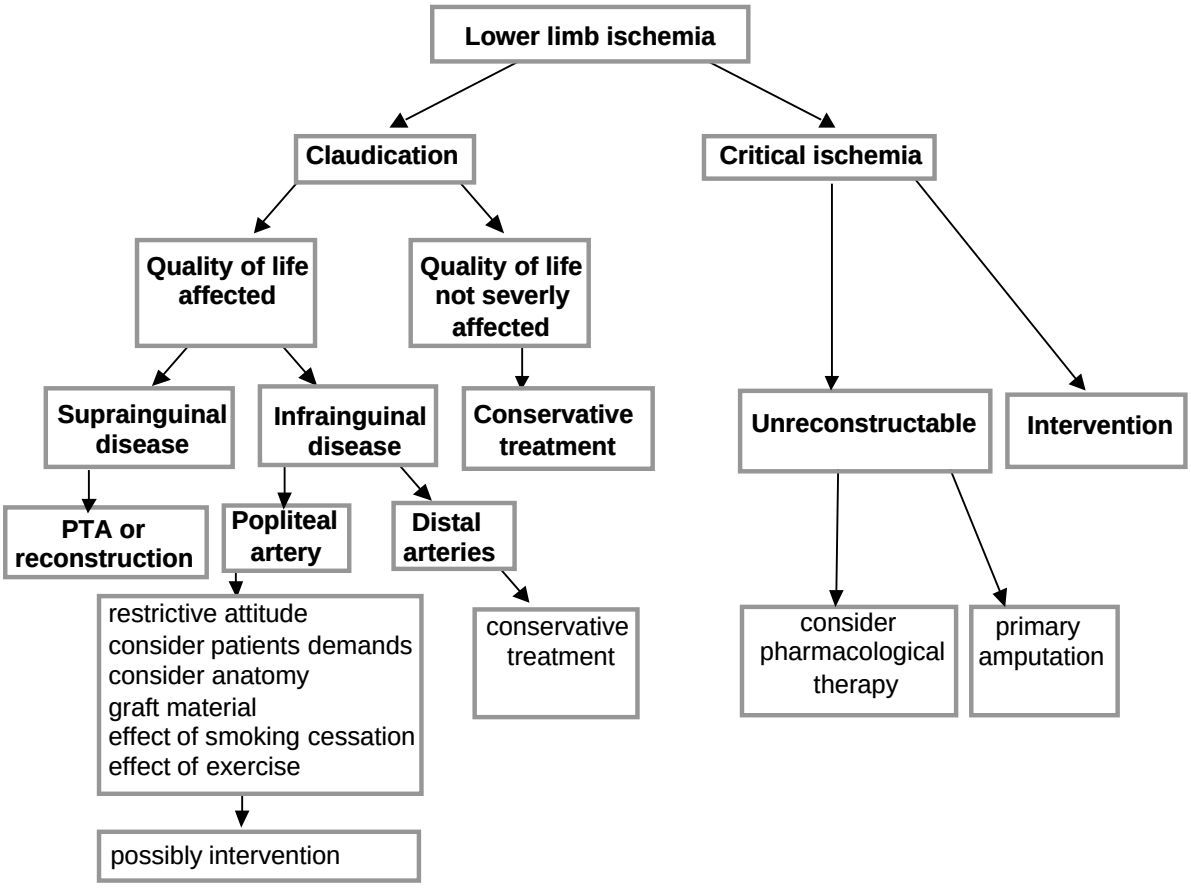
Prevalence of chronic lower limb ischemia

Reported LLI prevalence rates vary from 1-25 % depending on country, age group, diagnostic criteria and methods chosen. [9, 58, 66, 77-79] The majority of prevalence reports focus on IC, and show a higher prevalence in men than in women. They also describe a strong association between increasing age and prevalence. Few studies include persons above 75 years of age and the prevalence of critical ischemia is rarely described. It has been suggested that the disease is less severe in women compared to age matched men and that fewer women with LLI are correctly diagnosed by general practitioners. [65, 80]

The most recent prevalence report from Northern Europe found similar IC rates (1.1 %) for women and men (40-69 years). [77] The first report from Edinburgh showed similar prevalence rates for women and men (4.5%). [78] The Vadstena report showed a small but insignificant gender difference (3.8% in women vs 4.5% in men). [79] In the second Edinburgh report, and reports from Framingham, Limburg and San Luis Valley the prevalence of IC is higher in men. [9, 10, 65, 66] This gender difference decreases with increasing age.

In the Rancho Bernardo Study, which only included women, the prevalence of persons with an ABPI < 0.8 (asymptomatic and symptomatic PAOD) was 12%. A very strong relationship between increasing age and prevalence was reported, 9% of women 50-59 years old had PAOD and 21% of women 80-89 years old. [58]

Table 2. Therapeutic options in chronic LLI patients.



Natural history of chronic lower limb ischemia

Progression from IC to CLI or amputation is not inevitable. Less than 25 % of patients with IC will deteriorate to CLI and many claudicants will have continuous and unchanged symptoms. [63, 65, 81] The frequency of claudicants that eventually will be treated with vascular intervention varies in different reports, (3-18%). [66, 82] Accordingly, the patients' fear of amputation is often exaggerated, 4 % of diagnosed claudicants were amputated within 5 years in the Edinburgh material, and 1.8 % in the Framingham report. [10, 66] In 1244 male claudicants (mean age 65 years, 37% diabetes), the cumulative risk of amputation within 10 years was 10 %. The corresponding figures for development of rest pain and ulceration were 30% and 23%, respectively. [83] An important factor to consider when a patient has asymptomatic or symptomatic LLI is the 2-4 fold increased risk of cardiovascular mortality compared to the age matched population. [1, 10, 66, 79, 80, 84] This is probably a patient group where secondary prevention has a great potential to positively affect survival, as has been shown for CHD patients. [23, 24] Critically ischemic patients have a much higher risk of amputation and death, but few studies address this. In one study of unreconstructed patients, major amputation free survival was 28 % and overall survival was 46 %, one year after diagnosis. [85] Similar pessimistic outcome rates for unreconstructable patients have been reported by others. [8, 86]

Non-interventional treatment

It is important that all LLI patients obtain the best possible treatment for their concomitant diseases, such as diabetes, coronary heart disease or hyperlipidemia. These efforts may affect the progression of their LLI symptoms, in addition to an overall decrease in morbidity and mortality. Patients with LLI should be encouraged to stop smoking and if possible to exercise. Smoking cessation is one of the most important secondary preventive measures and has been reported to decrease the risk of developing rest pain and need for a vascular intervention, decrease the risk of coronary events and increase survival. [87] There is still a lack of larger randomised trials comparing the long term effects of exercise vs angioplasty in claudicants. Angioplasty is probably superior considering the improvement of the walking distance and the quality of life during the first six months, especially for suprainguinal lesions. [88-90] The long term effects of angioplasty vs exercise therapy are more debated. [88] Exercise therapy has been reported to improve walking distance, but also to lower cholesterol and decrease heart rate. [88, 89] In claudicants with infrainguinal disease, the risk of complications with angioplasty, the poor long term effects and the usually benign progression of IC, are all in favour of non-invasive treatment. [75, 88, 90-92]

There is a growing interest in pharmacological treatment of LLI symptoms. Internationally, drugs are available for such treatment, but in Sweden no such drug is approved for prescription. Cilostazol, a phosphodiesteras inhibitor, (inhibits platelet aggregation, antithrombotic and vasodilatating) increased quality of life and walking distances compared to placebo in claudicants. [93] It was equally effective for non-diabetic and diabetic patients and well tolerated. Pentoxifylline has also been shown to have some positive effects on symptoms, but the overall beneficial effects are modest. [93, 94] The effects of these drugs has to our knowledge not been analysed for women and men separately.

Selection for vascular intervention

The decision to treat a patient with vascular intervention is influenced by many factors. Depending on the patient, the lesion and the surgeon's preferences, preoperative evaluations can result in a variety of decisions: non-invasive medical treatment or vascular intervention; PTA or surgery; intervention or primary amputation. Table 2. Even if consensus documents for treatment of CLI patients exist today, the selection process is complex and great variations can be found. [63, 95] To our knowledge it has not been analysed with a gender perspective.

Vascular interventions for LLI

Time trends

It has been difficult to measure the exact number of patients treated with vascular interventions, particularly changes over time, mainly due to methodological problems. There are however some reports from Europe, North America and Australia on changes over time in the number of patients treated for LLI. [96-102] Table 3. The general trend is an increase in the number of surgical and endovascular interventions. Possibly a plateau is reached at approximately

Table 3. Changes over time in the number of vascular interventions.

Author (year)	Time analysed	Number of patients or interventions	Number of interventions / million inhabitants annually at the end of period observed	Time trend vascular intervention	Time trend amputation
Tunis (1991) 41 % women	1979-1989	30000 patients	240 PTA 650 arterial reconstructions 300 amputations	Increase	Plateau
Sayers † (1993)	1974-1990	2930 interventions	400 arterial reconstructions 1100 including amputation and PTA	Increase	Plateau
Pell † (1994)◆◆	1986-1990	555 interventions (arterial surgery+amputation)		Increase	Plateau
Ebskov † (1994)	1976-1990	5.1 million	380 arterial reconstructions 250 amputations / million	Increase	Decrease
Lepäntalo † (1996)	1976-1992	6500 interventions	967 estimation 300 interventions for LLI	Increase	
Hallett (1997) 43 % women	1973-1992	1100 interventions	1100 arterial reconstructions and	Plateau	Decrease
Mattes ◆ † (1997)	1980-1992	13644 interventions on 8600 patients Population 1.7 million	2664 by pass, 2200 PTA, 1400 TEA, 1800 amputations estimation 290 interventions /million	Plateau	Decrease

◆ annual number of interventions not presented.
◆◆ 500 annual referrals, population unknown
† ratio men / women not mentioned.

1000 interventions/million inhabitants. [100] The proportion of the general population that is treated for LLI varies in different countries. In Australia, 290 interventions/million inhabitants in 1992 were reported as compared to 1100 in the US for the same year. [100, 101] This can be explained by different prevalence rates, methodological differences and different Health Care systems.

The possibility that an increased number of vascular interventions reduces the number of amputations has been debated among vascular surgeons. One of the main objectives with vascular interventions for CLI patients is to minimise the risk for primary amputation. [63] Therefore the combination of decreasing major amputation rates together with the described increase of vascular interventions, could indirectly support the benefit of vascular interventions from a general health perspective. Such trends have been reported from several countries but the connection has been debated. [98, 100, 103, 104] It is plausible that a minimal number of vascular interventions must be performed in order to obtain a corresponding decrease in amputation rates. [100]

Even if changes over time in the distribution of suprainguinal vs infrainguinal interventions may have occurred, it is rarely analysed separately. This distinction is of potential importance for health care planning and economic forecasting, due to the already mentioned differences in basic characteristics between the two groups. Figure 1.

A dramatic increase in the number of PTAs performed over time has been described. [105-107] According to clinical observations women seem to constitute a growing proportion of the patients treated for LLI. Such possible changes over time in the number of treated women have received little attention. Table 3. This should be compared to the great number of reports in the literature, published in the 1990s, on changes over time in the number of women treated with coronary artery bypass surgery. [108-112]

Considering the expected growing proportion of women among treated LLI patients and that women possibly have other pre-operative conditions and needs than men, more efforts should be made to improve our knowledge of this hitherto rather neglected field of research.

Women treated for LLI

Very few investigations on LLI patients focus on treated women. The limited information available today is from retrospective investigations with small numbers of patients, in which women occasionally are analysed as a subgroup.

In a majority of reports on infra- as well as on suprainguinal interventions, women are in a minority (6-47%).[14, 73, 100, 107, 113-116] They are also 3-6 years older [7, 13, 14, 68, 73, 74] and have more diabetes than men. [3-5, 14, 74, 85, 114, 115] Furthermore women have the same or a higher rate of CLI vs IC as indication for treatment. [7, 14, 73, 76]

This implies that women have several factors that independently of their sex could influence referral patterns, preoperative risk evaluation and outcome.

Outcome

Preoperative conditions affecting outcome

In the preoperative assessment, the benefit of an intervention is weighed against the risk of complications and the patient´s expected survival. Several factors influence this risk, some of which are listed below.[5, 8, 13, 14, 67, 68, 70, 73, 74, 114, 117, 118] Table 4.

Outcome measures

The most commonly used outcome measures after vascular interventions are thirty-day and long-term survival, amputation and patency. These can all be influenced by the factors listed in Table 4.

In many reports, as mentioned previously, women have a higher rate of risk factors, such as diabetes, CLI and longevity. The higher mortality and amputation rates and the poor patency reported for women must therefore be analysed with special reference to these factors.

Survival

The mortality in LLI patients, regardless of treatment, is generally higher than the mortality in the age matched population. [1, 9, 66] A vascular intervention brings a risk of mortality in the peri- and postoperative period, especially for patients with a high prevalence of associated disease. This is reflected by a thirty-day postoperative mortality rate of 0-6 % in LLI patients. [13, 44, 70, 119, 120] Long-term survival rate is not an efficacy variable of the intervention performed, it rather reflects the frequency of associated diseases in the study population.

Women have higher postoperative mortality rates than men in many reports, but being female is not found to influence the risk of death when other factors, such as age, are considered in the analysis. [5, 8, 68, 73, 74, 117, 121, 122]

Mortality rates one year after infrainguinal interventions vary between 12-26%. [5, 8, 68, 74, 123] A lower mortality is reported after suprainguinal reconstructions, which is probably related to the lower mean age of these patients (4-10 %).[44, 71, 72, 121] Five year mortality rates are 26% among patients treated for suprainguinal disease and 66% for patients treated for infrainguinal disease, indicating that this group of patients has a more generalised disease. [8, 13, 71, 100, 114, 116, 117, 119]

Amputation

Postoperative amputation rate is an adequate outcome variable for the efficacy of interventions for LLI. In patients treated for LLI, and especially CLI, the risk of a subsequent amputation is relatively high. The risk is closely related to the presence of previously mentioned risk factors. The reported high risk of postoperative amputation in women often “disappears” in multivariate analysis. [5, 13, 68, 73, 74, 100, 114, 117, 124]

Table 4. Factors that could influence the result after an intervention.

Lower risk	*Higher risk*
Non-diabetic	Diabetic
Non-smoker	Smoker
No cardiovascular disease	Cardiovascular disease
Younger	Older
Claudication	Critical ischemia
Suprainguinal disease	Infrainguinal disease
Femoropopliteal disease	Femorodistal disease
Autologous vein graft	Synthetic graft
PTA	Vascular reconstruction
Stenosis	Occlusion
Short lesions	Longer lesions
First intervention	Redo surgery
Male ?	Female?

Amputation rates one year after infrainguinal interventions vary between 4-29%. [4, 74, 118] In patients treated with surgery or PTA for suprainguinal disease amputation rates are similar in women and men and generally lower (0-7%). [44, 71, 121] In CLI patients treated with PTA for suprainguinal or infrainguinal disease, the proportion of amputated patients one year after the intervention varies between 11-32%. [106, 107, 125-127]

Patency

The definition of patency varies widely among different studies, from angiographic evidence of a patent graft to the surgeons estimation based on clinical findings. As an outcome measure, it can be regarded as a "surrogate" variable, because patients may deteriorate in spite of a patent graft and occasionally also improve despite graft occlusion. Patency verified by duplex sonography or ABPI increment of more than 0.15 compared with a preoperative value are frequently used. [5, 13, 68, 118, 120, 128]

Early graft occlusion or thrombosis during the first postoperative period is often related to preoperative anatomical conditions and technical failure. Women have lower patency rates than men, which may be caused by the higher frequency of venous disease in women limiting availability of adequate grafts. Another contributing factor may be the smaller diameters of the female arteries. [68, 70, 118] The higher incidence of diabetic disease in treated LLI women and their more severe arterial disease may also affect the patency rate.[13, 14, 68, 70, 122] Late graft occlusion or stenosis is related to neointimal hyperplasia, a local physiological reaction. It has to our knowledge not been investigated from a gender perspective. A lower patency after vascular interventions has been described in women treated with HRT, compared to non users. [129, 130]

Amputation rates, the number of secondary minor or major vascular interventions or quality of life aspects are as mentioned not directly related to patency rate. An example of this is the contradictory circumstance that while women have poor graft patency in comparison with men, the amputation rates in the same studies nevertheless remain similar. [13, 68, 70, 122] From a patient point of view the limb salvage rate or preferably the major amputation free survival is more important as a measure of success than is patency. Studies using quality of life measurement as efficacy variables for intervention have emerged during the last decades. [131, 132] Society as a whole also has an interest in finding better tools from the point of view of health-economics in order to objectify our results. This development is promising, but the methods may need further adjustment before they can be used more widely in clinical practice. [131-136]

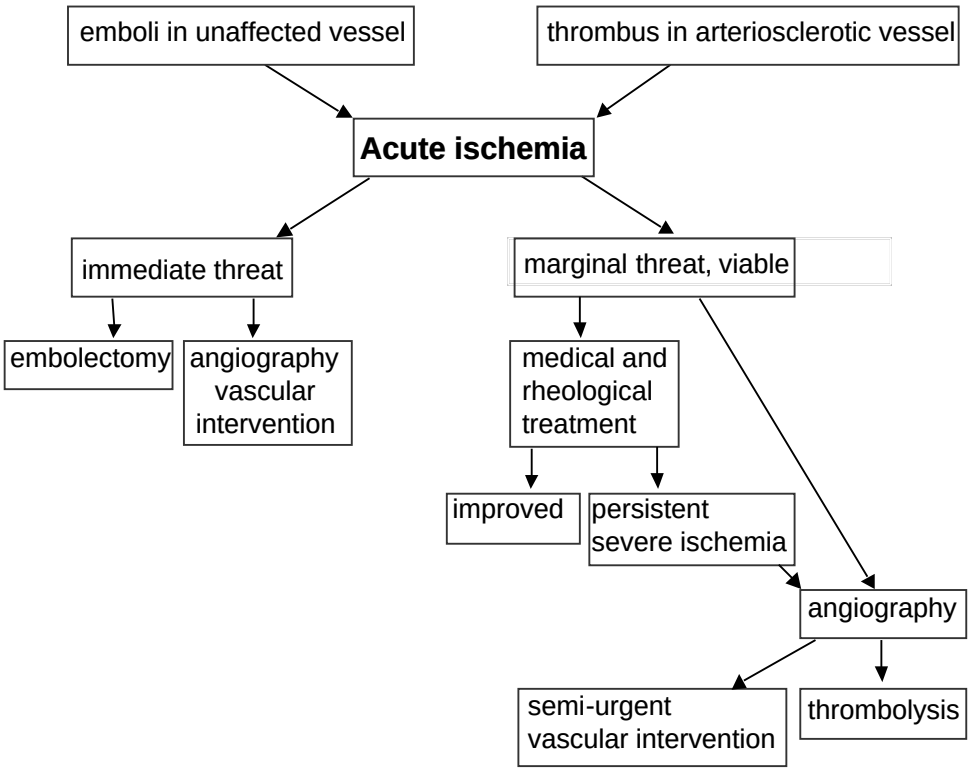
Acute lower limb ischemia

The concept of acute lower limb ischemia includes a range of conditions from acute embolic occlusion of a previously healthy vascular bed (acute ischemia) to acute aggravation of symptoms due to thrombotic occlusions of collaterals in a leg with already severe arterial occlusive disease (acute on chronic ischemia).

In the former case, the extremity is usually immediately threatened and urgent embolectomy is required. For the latter optimal management consists of anticoagulant treatment and occasionally a semi-urgent vascular intervention. Table 5.

Acute lower limb ischemia is usually caused by embolisation of thrombus from the heart due to atrial fibrillation or acute myocardial infarction. The risk of subsequent amputation and death is high. Common estimates are an amputation rate of >10 % and a 20-30 % mortality within 30 days postoperatively. A growing awareness among surgeons of the importance of differentiating between the acute ischemic and rapidly deteriorating chronic LLI has been described. [137]

Table 5. Therapeutic options in patient with acute ischemia.



AIMS OF THIS THESIS

The overall aim of this thesis is to describe and identify factors specific to women treated with vascular interventions for lower limb ischemia (LLI).

The aims of the four papers were to investigate:

I changes over time in the proportion of women treated for LLI and possible gender differences in the localisation of treated lesions.

II gender differences in amputation and survival rates and changes over time in patients treated for LLI.

III gender differences in pre-operative conditions, localisation of lesions treated and postoperative results in patients treated for CLI.

IV the reproductive history in women treated for LLI.

PATIENTS AND METHODS

Paper I- IV

In this thesis patients treated for LLI between 1970 to 1996 at the Karolinska Hospital and in the County of Stockholm were studied. Basic characteristics of the investigations performed and patients included are presented in Table 6.

Paper I , II

The register of the National Board of Health and Welfare (NBHW)

All patients treated in Swedish hospitals are recorded according to the International Classification of Diseases (ICD) in a computerised register controlled by the National Board of Health and Welfare (NBHW). All deaths are recorded in the Swedish Cause-of-Death Register, also controlled by the NBHW. During the observed period the ICD 8 (1970-1979) and 9 (1980-1994, revised 1987) were used in Sweden. Table 6. All operative ICD-codes representing vascular and endovascular interventions and amputations for lower limb ischemia (LLI) during 1970-1994 in the County of Stockholm were extracted. Table 6. Before 1979, the classification system for vascular surgery did not specify the localisation of lesions treated. The main categories were embolectomy, thrombectomy, thrombendarterectomy and arterial by pass operation, after 1979 the ICD codes are more detailed.

Table 6. Data on the four papers.

	Paper I, II	**Paper III**	**Paper IV**
Type of study	Observational population based	Observational	Case-control
Study base	County of Stockholm	The Karolinska Hospital	The Karolinska Hospital, hospital catchment area
Data collected from	NBHW	Hospital records	Questionnaires and hospital records
Time period	1970-1994	1993-1994	1994-1996
Follow-up	Until 1998	Until May 2003	-
Patient group	Patients treated for LLI	Patients treated for critical ischemia	Women treated for LLI, women in the population
Number of subjects	8600	119 women 115 men	116 patients 197 references
Missing cases	-	7 women 5 men	57 patients 151 references
Number of interventions	12295	191 in women 173 in men	-
Proportion women	44 %	51%	All

Validation

Data on vascular interventions from the NBHW register has not previously been validated. Therefore a random sample of 644 patient records (5%) from the patients' first vascular intervention or amputation performed during the observed period was chosen for validation. The purpose was to investigate the accuracy of the register by comparing extracted data with hospital records. Records for 546 patients were found (84.8%). The remaining 98 patient records were not retrievable despite extensive efforts. Analysis of the 98 missing records indicated that significantly more records were missing from the beginning of the observation period (15% of all missing records originate from 1970-1974 vs 8% of records retrieved, p=0.002). Mean age and sex were comparable in missing and retrieved records (p=0.5, p=0.06).

Comparison of data in the Register and discharge notes revealed 13 faults (2%) in the Register, mainly regarding the duration of hospital stay. When the data in the Register were compared with the Surgery charts, 4 faults were found in the Register, 3 of which was double coding for the same procedure.

Accordingly, while 26 % of the validated records had missing or incorrect data, only few faults were found in the Register. The computerised control system in the Register, not accepting non-existent or incorrect codes or personal registration numbers may account for this result. This analysis suggested that we could consider the data extracted from the Register to be reliable.

Limitations

The two most important systematic errors to take into account when interpreting data in the Register are the accuracy of data and missing cases. The validation of the Register showed few errors.

The possibility of patients being treated without this being recorded in the NBHW was probably higher during the first 10 year period. The financial situation in the hospitals in the later period forced health care providers to record treated patients in order to receive funding, minimising the risk for missing cases.

Paper III

Patients and methods

All vascular or endovascular interventions performed for arterial occlusive disease of the lower extremity were identified in surgery charts and the Register of the Department of Radiology. They were extracted with the patients' individual registration number. Only patients with CLI were included in the study. Table 6. CLI was defined according to the TASC document. [63] Medical records were obtained from the hospital archives and the information was recorded on a data sheet.

Paper IV

Patients and references

All women treated for LLI in 1994-1996 at the Karolinska Hospital were included. A random retrieval of women within the same age range (40-90 years) as the patients, living in the hospital catchment area was extracted from the "National Swedish Person and Address Register" (SPAR). While being in the same age range, this cohort had a lower mean age than patients (61 years vs. 69 years). Table 6.

Method

A validated questionnaire was mailed to patients and references together with a covering letter explaining the aim of the study with an enclosed prepaid envelope. Women who did not respond within 3-5 weeks, received one reminder phone call. The questionnaire consisted of 30 questions, divided into four sections; marital status; reproductive history; vascular and medical history.

STATISTICS

Paper I-IV

Comparison between group means was performed with Students t-test or with one-way analysis of variance (ANOVA, F-test). Distribution of categorical data between the groups were tested with the χ^2 analysis.

Long term survival and thirty-day survival were analysed using the Gehan-Wilcoxon statistic (paper I, II). Multivariate survival analysis and risk factor analysis for amputations were performed using the Cox regression model with the Wald statistic.

To separate possible differences in age and gender, an analysis was performed by age adjustment besides the regression model. Age-adjustment was performed by adjusting the number of amputated women in every five-year age group to the age of men in Stockholm during the same five-year period (paper I, II).

The time to amputation or death was analysed using a Cox regression model considering age, sex, diabetes, cardiovascular disease, the severity of disease (rest pain vs ulcers) and localisation of lesions treated (paper III). The mortality rate from the date of surgery until 31 April 2003 was also compared with the mortality rate in the general population of the same age, by calculating the standardised mortality ratio (SMR), i.e. the ratio between observed and expected numbers of deaths. A match for age and concomitant diabetes at the first qualifying intervention was performed in women and men, with random numbers using Excel software. A woman was used as standard, matching the first man of the same age with the lowest random number.

The influence of age on medical history was evaluated by logistic regression analysis, including the factors; age, type of disease or risk factor and being a patient or reference (paper IV). To account for differences in mean age, the number of patients and references in every five year age group who had used oral contraceptives were analysed separately. The difference in the use of oral contraceptives was also controlled by logistic regression analysis considering every five-year age group and smoking habits.

Statistical significance was defined as a *P* value less than 0.05.

RESULTS

Paper I

Time trend

The number of vascular interventions increased significantly ($p<0.001$) over time, from 18 per one million inhabitants in 1970 to 786 in 1994. Figure 2. The proportion of treated women grew from 34 % to 48 % during the analysed period ($p<0.001$). Mean age increased from 63 years in 1970-1974 to 71 years in 1990-1994. In 1970-1974, the gender difference in mean age was small (63 years for women vs 62 for men). This changed to a six year age difference in the last five-year period (74 years vs 68 years, $p<0.001$). The age difference between the sexes varied with type of procedure. Table 7.

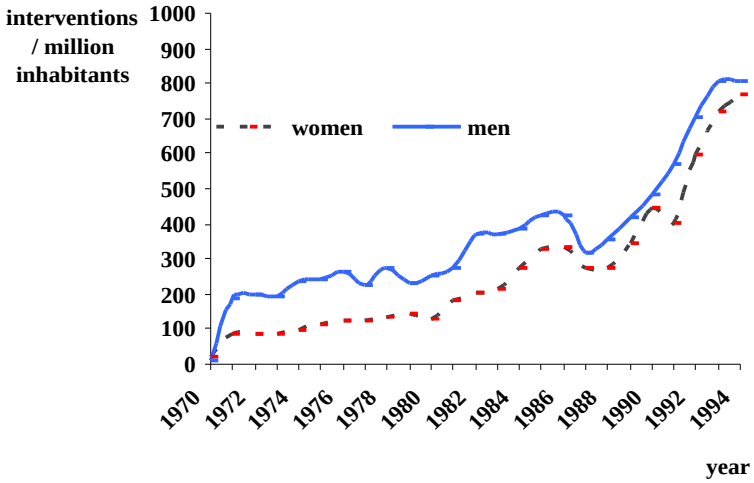


Figure 2. *All vascular interventions from 1970 to 1994 presented as annual number per one million inhabitants for women and men.*

Table 7. Mean age, defined as age at first vascular intervention, for women and men, standard deviation for each procedure type. Annual incidence of operations per one million inhabitants. The percentage of interventions performed on women during each five year period is presented in brackets.

		Mean age	*1970-1974*	*1975-1979*	*1980-1984*	*1985-1989*	*1990-1994*
Suprainguinal	women	68.2, ± 11.3	-	-	51(34)	79 (41)	96 (41)
	men	64.9 ± 10.5			101	112	135
Femoropopliteal	women	73.3, ± 9.7	-	-	22 (33)	49 (40)	123 (48)
	men	68.2, ± 9.8			45	73	135
Femorodistal	women	76.1, ± 10.3	-	-	3 (33)	12 (34)	49 (43)
	men	70.6, ± 10.1			6	23	65
Embolectomy	women	77.8, ± 11.8	30 (45)	43 (40)	75 (47)	77 (55)	77 (56)
	men	71.3, ± 11.7	36	64	84	64	60
All vascular interventions	women	71.1, ± 14.1	80 (33)	115 (35)	205 (38)	309 (44)	588 (47)
	men	66.1, ± 12.6	165	215	333	398	675

Chi square analysis for trend, analysing the proportion of interventions performed on women over time was significant for all groups ($p<0.001$).

Type of procedure

During the last 15 years the number of vascular interventions increased rapidly and the distribution between types of procedure changed for women and men. Table 7. The most rapid increase was found in the number of PTAs and infrainguinal procedures in both women and men.

The reduction in the number of embolectomies performed after 1980 was mainly explained by the decreasing number of such operations in male patients.

An estimate of the future number of vascular interventions was also performed. A regression analysis, based on the number of interventions performed during 1985-1994, estimated that 1550 interventions per one million inhabitants will be performed in 2010. A prediction of the number of femoropopliteal by passes showed that in 2005, the majority of patients treated will be women .

Paper II

Survival

Women and men treated with suprainguinal, femoropopliteal and femorodistal procedures had similar thirty-day postoperative survival . The thirty-day survival rate was worse for embolectomised women when compared to that for men. Table 8. Increasing age and calendar years of treatment (1975-1979) were independent significant risk factors for poor thirty-day survival ($p<0.001$) in the multivariate analysis, but not female gender ($p = 0.17$).

Survival at 1, 3 and 5 years after the first intervention was worse for women than men ($p < 0.001$). Table 9. Fifty percent of women and 55 % of men were alive after 5 years, which can be compared to the expected five year survival of the Swedish general population of the same age, 88% for women and 87% for men.

In the univariate analysis, age, calendar years of treatment and female sex were identified as risk factors for postoperative death. Old age was the most important risk factor in the multivariate survival analysis, followed by having been treated in 1980-1989 and being male ($p< 0.001$).

Amputation

The percentage of amputated women and men in the entire patient cohort was similar (11.4% vs. 10.2%, $p = 0.075$). No differences between women and men were found in the percentage of amputated among living patients. Table 9.

Table 8. Thirty-day survival for the four subgroups is presented as the percentage of survived patients. The number of treated patients is also presented.

	Women (%)	*Men (%)*	*P value*
Suprainguinal interventions◆◆	94.3	94.6	ns
	n=876	n=1258	
Femoropopliteal bypass◆◆	97.4	96.5	ns
	n=733	n=863	
Femorodistal bypass◆◆	97.2	95.1	ns
	n=248	n=349	
Embolectomy◆	75.8	80.8	0.008†
	n=1119	n=922	

◆ 1970-1994
◆◆ 1980-1994
†Gehan-Wilcoxon statistic.

Compared to patients with intact limbs, amputated patients were older (73 years vs. 68 years, P<.001) and amputated women were older than men (76 years vs. 70 years, p<0.001).

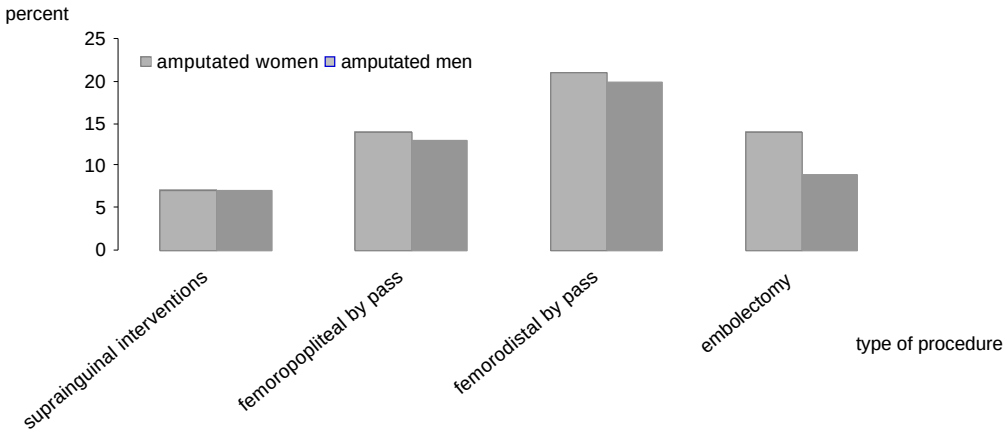
The most common procedure preceding an amputation was embolectomy (40%) in 1980-1984, which changed to infrainguinal intervention (51%) in 1990-1994. For women and men treated with femorodistal procedures a higher proportion was amputated than was the case with patients treated with other types of procedure (p<0.001). Figure 3. A higher percentage of amputated women in embolectomised patients was the only significant gender difference observed in the procedure subgroups (p <0.001).

Treatment performed in 1985-1994, old age and female sex were identified as risk factors for amputation in the univariate analysis. In the multivariate analysis, old age and calendar year remained significant but not female sex.

Table 9. The number of living women and men and amputated patients at 30 days, 1,3 and 5 years after their first vascular intervention. The percentage is presented in brackets.

Time after intervention	*Living women*	*Amputated women*	*Living men*	*Amputated men*
30 days	3420 (89)	123 (4)	4406 (92)	162 (4)
1 year	2877 (75)	324 (11)	3828 (80)	379 (10)
3 years	2378 (62)	386 (16)	3147 (65)	424 (13)
5 years	1918 (50)	413 (21)	2638 (55)	455 (17)

Figure 3. *The percentage of amputated patients in 1980-1994*



Pearsons chi square analysis for comparison between groups and between women and men.

Paper III

Patient characteristics

Women had a higher mean age at their qualifying intervention compared to men (74 years vs 70 years). There were less female diabetic patients and smokers (22% diabetic women compared to 43% men, p=0.0004, 63% smoking women compared to 82% men, p=0.005). All other risk factors were similar in women and men, also in the matched subgroup. An equal share of women and men had rest pain or ulcers/gangrene (54% of women had ulcers/gangrene vs 56% of men, p=0.77).

Localisation of lesions treated

The localisation of the treated lesions differed between women and men. Figure 4. A greater proportion of lesions was localised above the inguinal ligament in women, also after matching for age and diabetes. A similar distribution of more lesions suprainguinally in women, was also found when all interventions performed ipsilaterally were analysed. In 92% of the vascular reconstructions some kind of graft was used, autologous veins more often in men than in women.

Outcome

Most measured outcome variables, such as mortality and amputation rates, were similar in women and men over time. Table 10. The number of amputated women and men in the matched subgroup was also similar (11/80 vs 8/80, p=0.48). One year after the qualifying intervention, more men had improved, but fewer women attended the clinical control and were available for analysis. Table 10.

The time to amputation was not significantly affected by age, localisation of treated lesion, gender or diabetes. No correlation was found between the localisation of the treated lesion and amputation in matched patients (p=0.33 for women, p= 0.24 for men).

Time to death postoperatively for all patients and the matched subgroup was only influenced by age in a Cox regression model (p=0.004). No correlation between survival and localisation of lesions treated was found for women or men in the matched group (p = 0.60, p =0.07). Using a calculation of standardised mortality ratio (SMR), an excess mortality was observed, 174 deceased patients compared to the estimated 62 persons (SMR 2.53, CI 2.16-2.93).

Figure 4. *Distribution of procedure types in women and men treated for critical ischemia at the Karolinska Hospital 1993-1994.*

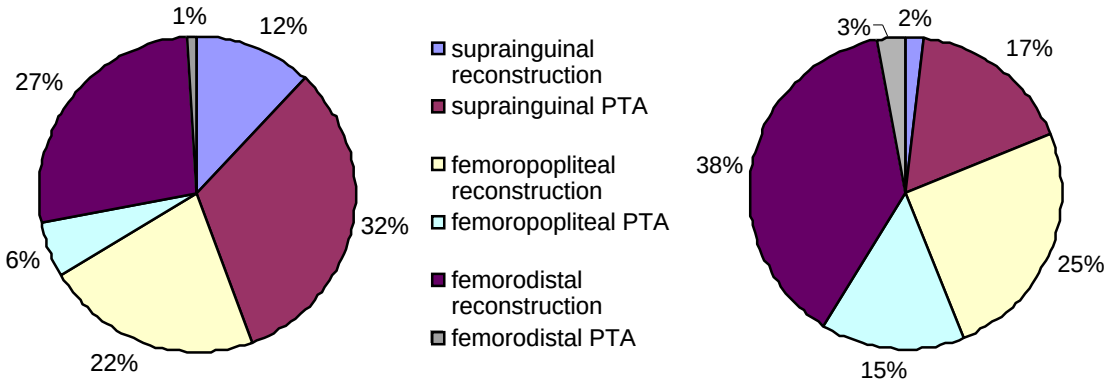


Table 10. Postoperative mortality. The number of amputated patients, second interventions and improvement 30 days, 1 year and 5 years after the qualifying intervention of patients alive. Outcome for all patients alive in May 2003 (9-10 years postoperatively) is also presented.

		Dead *n (%)*	P	***Amputated*** *n (%)*	***P***	***Second intervention †*** *n (%)*	***P***	***Improvement*** *n (%)*	***P***
30 days	*Women*	2 (2)	0.08	1 (2)	0.35	28 (24)	0.64	88 (74)	0.93
	Men	7 (6)		4 (4)		23 (21)		84 (73)	
1 year	*Women*	17 (14)	0.32	7 (7)	0.47	42 (41)	0.61	35 (34)◆	0.001
	Men	22 (19)		9 (10)		35 (38)		53 (57)◆	
5 years	*Women*	62 (52)	0.34	5 (9)	0.94	29 (51)	0.17	◆◆	◆◆
	Men	67 (58)		4 (8)		18 (38)			
May 2003	*Women*	88 (74)	0.34	1 (3)	0.14	19 (61)	0.25	◆◆	◆◆
	Men	85 (74)		4 (13)		14 (47)			

† *minor secondary procedures or major vascular intervention*

◆ missing patients, but alive ; 52 women (51%) and 33 men (35%), p<0.001.

◆◆no standardised clinical follow-up after 1 year.

Paper IV

Medical background and reproductive history

The social situation was similar for patients and references, as well as their body mass index (BMI). More patients had a history of smoking (88% vs 45%, p<0.001), diabetes (15% vs 4%, p=0.001), hyperlipidemia (24% vs 12%, p<0.001), MI (15%vs 2%,p<0.001) and angina (24% vs 5%, p<0.001) than references. Patients still had more concomitant disease than references in a Cox regression model considering age differences: MI, angina, and hyperlipidemia (p=0.1, p=0.01, p=0.08).

The age at menarche and menopause, number of pregnancies, hysterectomies and the use of HRT were similar between the groups. Table 11. The mean differences and confidence interval for age

Table 11. Reproductive history for patients and references. Number of women (percent).

	Patients n=116	*References n=197*	*P-value*
Menarche ◆	13.4 (S.D. 2.0)	13.2 (SD 1.5)	0.37
Pregnancies, mean	1.8	2.0	0.27
Null parity	21 (18)	25 (12)	0.19
1-3 pregnancies	86 (74)	155 (79)	0.31
≥ 4 pregnancies	9 (8)	17 (9)	0.79
Ever used oral contraceptives	18 (16)	105 (53)	<0.001
Premenopause	8 (7)	43 (22)	<0.001
Natural menopause	77 (66)	101 (51)	0.45
Unaware of age at menopause	15 (14)	23 (15)	0.48
Perimenopausal HRT	4 (4)	8 (5)	0.55
Surgical menopause	12 (11)	19 (12)	0.55
Mean age at natural menopause ◆◆	50.2 (S.D. 3.8)	50.4 (S.D. 3.7)	0.71
Hormone replacement therapy	46 (40)	85 (43)	0.55
Hysterectomy	17 (15)	25 (13)	0.43
SOE	15 (13)	23 (12)	0.51

◆ Mean difference 0.19, (95 % C.I. –0.61, 0.23)

◆◆ Mean difference 0.21 , (95 % C.I. –0.90, 1.32)

at menarche and menopause further confirmed that the groups were similar as to reproductive factors. More references had used oral contraceptives (53% vs 16% of patients) and more references had not reached menopause compared to patients, due to the lower mean age of this group. Table 11. The use of oral contraceptives for references was higher than for patients also when five-year age groups were compared. When age at natural menopause was analysed as four groups (menopause at <45, 46-50, 51-55 or >55 years), patients and references were distributed equally in all groups.

Patients treated for suprainguinal disease (n=73) were younger than patients treated for infra-inguinal disease (n=43), (62 versus 69 years, p<0.001). The medical and reproductive history of patients suffering from suprainguinal - and infrainguinal disease was similar, except for the smoking history (47 % versus 16%, p=0.004) and the use of oral contraceptives (21 % versus 7%, p<0.001).

In women who were under the age of 55 when answering the questionnaire, a higher percentage of patients (n=17) smoked, had MI and angina than women in the reference group (n=64). The reproductive history was similar apart from the use of oral contraceptives (47% vs 72%, p<0.001) and a higher number of nulliparous patients than was the case for references (35% vs12%, p = 0.03).

GENERAL DISCUSSION

Preoperative conditions in women

Age and reproductive history

The higher mean age in women treated for LLI (3-8 years) was one of the most important findings in our reports (paper I, III). Biological differences, such as a pre-menopausal protection of endogenous oestrogen can explain a later onset of disease in women compared to men. [2, 46, 133, 138] Many factors associated with the development and progression of arteriosclerotic disease are affected by oestrogen levels, as mentioned previously .[27-29, 32, 139] A different reproductive history, affecting endogenous oestrogen levels throughout life could hypothetically influence the development of LLI.

This was not supported by the data in our report (paper IV). Women with LLI did not have a different reproductive history from that of women from the general population (paper IV). Age at menopause is the most important reproductive factor in the literature concerning the association between reproductive history and CHD. [38, 42, 43, 46, 140] In Weiss' investigation of women with aortoiliac disease, more patients than controls had a history of an early surgical menopause (<43 years). [45] Cronenwett found a higher number of pre-menopausal women in his material of 75 women with aortoiliac disease, compared to the estimated number, but the difference was not significant, 34 % vs 22%. [44] In our analysis of women with an early onset of LLI or suprainguinal disease we did not observe a lower age at menopause compared to that reported for references (paper IV). The reliability of our data is limited because of the small sample in the subgroup analysis. Smoking lowers the onset age for menopause with approximately 1-2 years. [18-20] If this is applied to our data, the patients would actually have had a higher age at menopause than women in the population. Our observation of more nulliparous younger patients should also be interpreted with caution due to the size of the subgroup (paper IV). It may reflect a higher frequency of smokers or that these women have a different social situation. Among the other reproductive parameters in our report, only the use of oral contraceptives differed between the groups. This could be interpreted as if use of oral contraceptives protects against development of disease, a finding that has been reported in animal models.[141, 142] The opposite has however been shown in studies on patients with CHD and ischemic stroke, as well as a recent report on peripheral arterial disease, the RATIO trial. [51, 53, 54, 143, 144] The RATIO trial reported that women with PAOD (n=152) had a significantly higher use of oral contraceptives than the controls (51 % vs 38 %). The women with PAOD, defined by ABPI measurement, angiograms and questionnaires, who were included in this study, were surprisingly young (mean age 44 years, range:25-49 years) but they were still considered as having arteriosclerotic disease. This could partly explain the contradictory findings as compared with our report. These women did probably not suffer from the common form of more age-related arteriosclerotic disease, why the results cannot be generally applied on all women with LLI.

The lack of other differences in reproductive history in our report and the contradictory findings in the literature on CHD may be explained by methodological difficulties.

Hypothetically oestrogen could affect coronary or carotid arteries differently than other peripheral arteries. Our results indicates that other risk factors are probably more important for LLI development in women at risk than the reproductive history.

As expected, all the well known risk factors and cardiovascular disease were more common in women treated for LLI than in women in the population (paper IV).

A different risk factor profile for women probably also contributes to the later onset of disease in women compared to men. [10, 15, 145] Women treated for CLI did not suffer from more cardiovascular disease than men and they smoked less during the observed period (paper III). Data on smoking habits, however, are known to be unreliable in retrospective studies of this kind, and should always be interpreted with some caution.

The number of female smokers among LLI patients will certainly change, since an equal number of women and men smoke today in the society, 20% - 25%. [146, 147]

Selection and referral

Very little is known about referral patterns in LLI patients with regard to gender. An attempt to identify some possible explanations for the described differences in the treatment of women and men with LLI is presented below. Possible explanations for the later onset of disease in women have been discussed above. An overall underestimate of the prevalence of the disease in the population has been reported, and more women are found among asymptomatic LLI patients than in symptomatic patients. [80, 81, 148] Women with CHD present with atypical symptoms and uncharacteristic ECG changes in comparison with men. [23, 110, 111] A missed diagnosis for AAA patients occurs more frequently for women than for men, regardless of age. [149, 150] Socio-economic disadvantages have been reported to influence the risk of CHD in women. [151] This can hypothetically also affect willingness among women to seek healthcare and consequently to be correctly diagnosed. In addition, problems of communication between female LLI patients and male vascular surgeons may exist. Differences between women and men with regard to levels of expressed discomfort or pain as well as different perceptions of quality of life restrictions caused by IC may also occur. This can delay the diagnosis or referral of women compared to men. There is no consensus about the indication for vascular intervention in IC patients, which can increase the risk that women are offered treatment less frequently. Table 2

In patients treated at our clinic for CLI, the number of outpatient visits before an intervention was similar for women and men (paper III). If there is a bias in selecting women with CLI for vascular intervention, our data indicate that this probably occurs prior to referral to a vascular surgeon.

Women treated for LLI suffer from a heavy load of associated diseases compared to other women, but not more than is the case for treated men (paper III, IV). Their greatest disadvantage when the preoperative conditions are evaluated is their older age. It is probable that the main explanations for this is biological combined with a different risk factor distribution. More efforts should be made to identify other biological factors for the later onset of disease in women besides their reproductive history.

Vascular interventions in women

Increasing number of women treated for LLI

The increased number of interventions performed during the observed 25 years

described in our Stockholm study corresponds to other reports (paper I). [96, 97, 99, 102, 136, 152] Table 3.

The growing proportion of female patients over time has not been described previously and the distribution of procedure types has never been analysed with a gender perspective (paper I). An increasing prevalence of LLI in women, due to their changing smoking habits and a growing prevalence of diabetes, can explain this increase. The increasing mean age in the population may also be a contributing factor. [146] This will certainly affect the future workload of vascular surgeons. The rapid change in the proportion of women can also be explained by an increasing awareness that women can suffer from LLI, and by the fact that more women are being referred to vascular surgeons.

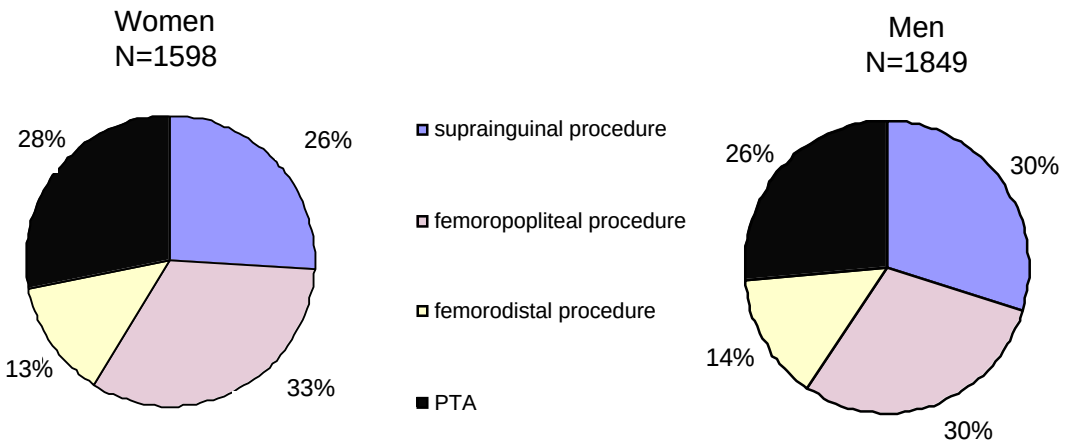
Undoubtedly, one of the most important factors for the dramatic development from 1970 to 1994 is the wider indication for treatment. [96, 99] The latter is probably related to the development of and improvement in endovascular and surgical techniques. Improved outcome and lower complication rates may have diminished the restrictive attitude towards treating the elderly, which is especially beneficial for women. [100, 117, 153]

Fewer women than men are treated

Although increasing numbers of women are treated, women were still in a minority in 1994 (46%) (paper I). The lower number of women is supported by many reports on patients treated for LLI or IC (6 %- 36%).[13, 73, 107, 114, 125, 154, 155] This may reflect a lower prevalence in women, but this is unlikely considering their age. Female claudicants may have lower psychical demands than men have, a hypothesis supported by the higher number of "asymptomtic " cases reported among women. [65, 80] It is unlikely that women with CLI would be denied intervention if anatomically possible. Accordingly the sex ratio was similar in our report to that in many others reports on CLI patients (paper III). [5, 68, 106, 115, 119, 126, 127, 156, 157] The literature is however contradictory. The most likely explanation for a lower of number treated women in some CLI reports is different study populations. A lower prevalence of CLI in the female population and more advanced distal disease in women may also contribute. [7, 113, 128, 158]

Although fewer women were treated between 1990 and 1994, the distribution of types of procedures for chronic LLI was similar for women and men. Figure 5.

Figure 5. *Proportion of women and men treated for lower limb ischemia with suprainguinal procedures, femoropopliteal or femorodistal by pass and PTA in 1990-1994 in the county of Stockhlom*



Changes from 1994 to 2002

Since 1994 the proportion of women has changed in the county of Stockholm. In our first Stockholm study, we predicted that a majority of patients treated with femoropopliteal by pass would be women by 2005 (paper I). When this thesis was written we extracted data from another source, SWEDVASC, in order to evaluate if this prediction was accurate. The vast majority of vascular surgeons record basic data on vascular interventions performed and on treated patients into this nation wide vascular register. The data extracted from SWEDVASC showed that already in 2002 a majority of patients treated for LLI in Stockholm was women, 358 women vs 330 men. Table 12.

Interestingly, the types of procedures for patients treated for LLI were still almost similarly distributed in women and men in 2002.

Table 12. Vascular interventions for LLI in the county of Stockholm 2002 (SWEDVASC).

	Women	*Men*
Suprainguinal disease		
Vascular reconstruction	50	43
PTA	91	78
Femoropopliteal disease		
Vascular reconstruction	54	63
PTA	52	34
Femorodistal disease		
Vascular reconstruction	104	109
PTA	7	3
TOTAL	358	330

Localisation of treated lesion

Suprainguinal interventions did not increase as dramatically over time as infrainguinal interventions in Stockholm (paper I). In this report a stable proportion of female patients, 41%, was observed, similar to other reports (33% - 42%). [44, 72] Patients with suprainguinal disease in Stockholm and in our report on reproductive history were similar to those described by others; they were younger, smoked more and had a better outcome than those with infrainguinal disease (paper I, II, IV). [44, 67, 72] Among our CLI patients, 45 % of the women and 19 % of the men were treated for suprainguinal lesions (paper III). In the reports by Molloy and Nasr on PTA treatment of CLI, 14% –23% of the patients, with no gender specified, were treated for suprainguinal disease. [106, 127] An Italian group, reporting on outcome for CLI patients (27% women), had a population in which 39% were treated for suprainguinal disease. [113] These data are more in accordance with our female subgroup (paper III). It is difficult to find one single explanation for the high number of suprainguinal interventions among our women suffering from CLI. It may reflect a higher prevalence of suprainguinal disease in women, but the most probable explanation is that most patients with CLI have multilevel disease. As previously discussed, women with CLI could have infrainguinal anatomical conditions not allowing further intervention. This finding suggests that patients with suprainguinal disease actually fall into two separate groups; the young, smoking claudicant with a limited localised lesion and the older patient with multilevel disease. Figure 1. It is possible that the pathogenesis of the arteriosclerotic disease differ in these patients. [44, 67, 72] The angiograms performed in women treated with suprainguinal interventions in our report on reproductive history were not analysed in detail within the study protocol. It is possible that the lack of differences in age at the onset of menopause between women treated for supra- and infrainguinal disease in that report, is due to a number of women classified as “suprainguinal”, that actually had multilevel disease (paper IV).

The increase in the number of *infrainguinal procedures* over time was more dramatic than for other analysed groups in the Stockholm study (paper I). The improved surgical techniques and wider indications, treating IC, CLI and elderly patients, are probably the most important explanations for this. The willingness to treat elderly, best reflected by the increase in mean age over time, is probably the main explanation for the increase of treated women in this subgroup (paper I). [100, 124] The described advantages of vascular intervention compared to primary amputation from a patient perspective and health-economical point of view has certainly also influenced this rapid increase. [131, 136, 159, 160] An awareness among surgeons that "acute on chronic" ischemia should preferably be treated with semi-urgent infrainguinal intervention rather than with an immediate embolectomy may also have contributed to the increasing numbers (paper I).

The lower number of women treated with femorodistal by passes compared to the number of men can be explained by anatomical differences. [68, 70, 118, 161] Smaller lumen areas, too distal disease or lacking vein grafts in women may influence the surgeon's ability to intervene. This is supported by an investigation of amputations at the Karolinska Hospital in 1992. A higher proportion of women was rejected for intervention by vascular surgeons than was the case for men.[162]

The ICD code for *PTA* was first used in Stockholm in 1987 and analysis over time was therefore not meaningful (paper I). Between 1990 and 1994, 18 % of all interventions performed were PTA and a similar number of women and men were treated (447 women vs 488 men).

In some PTA studies, the outcome has been analysed with a gender perspective but no differences in survival or limb salvage rates were found. [122, 125, 126, 157] In several other reports on the results after PTA, the number of treated women and men are not presented or analysed separately as regards the localisation of lesions and outcome. Is this a reflection of the importance of considering anatomy, age and diabetes rather than gender? [105-107, 158, 163] It may of course also be an effect of the low power accomplished when subgroups are analysed.

The indications for PTA are wider today. Some reports show that PTA, not vascular reconstruction, constitute 69 % of the primary interventions performed for CLI. [105, 106] The use of PTA for infrainguinal lesions has increased, although knowledge of patency and outcome is limited. [106, 125, 126, 157]

Outcome

At first, women in our Stockholm investigation appear to have a higher mortality and amputation rate than men. When age was considered, it became clear that women had similar or even better outcome after interventions than men.

Survival

The postoperative thirty-day survival after supra- and infrainguinal interventions in Stockholm was similar for women and men (paper II). It can be expected that the higher mean age in women (3-5 years) results in a higher mortality rate in women. This was not found to be the case and therefore one can speculate if the preoperative conditions differ for women and men. This hypothesis is supported by our report on CLI patients, among whom more men than women were smokers and had diabetes (paper III).

The poor long term survival rate in comparison with the general population, as well as the strong influence of increasing age on survival rates was expected (paper II). The higher mortality in women compared to men, i.e. 1, 3, and 5 years after the first intervention, is in agreement with other studies. [13, 14, 114] When the age difference between the sexes was considered, male sex was an independent risk factor for death. This was highly unexpected. It can be a consequence of the better survival rate in women in general, but again it could be explained by a selection bias, with a more liberal attitude when treating high risk men. Male sex as a risk factor for death in treated patients, has to our knowledge previously only been described by Al-Omran, in his population based investigation on outcome after interventions performed for PAOD 1991-1998 in Ontario. [117] Unfortunately no explanations for this unexpected finding are present, only references to rates in untreated patients. The cohort does not differ in any obvious way from ours or that in other reports on outcome for treated LLI patients. In the majority of reports however, gender is not a risk factor, once age and other factors are considered. [5, 8, 68, 73, 74, 121, 122]

Survival rates are often presented as if this outcome variable is related to the intervention performed in patients treated for LLI. The observed high mortality rate compared to the expected rate in the population, is more related to the overall risk of premature death due to cardiovascular disease than the actual intervention. Hypothetically, survival rates in LLI patients could even be improved by successful intervention, due to increased mobility and ability to exercise. An improved quality of life as a result of reduced pain and improved ulcer healing may reduce stress and blood pressure. This is however difficult to evaluate, as others have observed. [8, 104]

Amputation rates

As has been found in other studies our Stockholm study revealed that women ran a higher risk of subsequent amputation than men [7, 115] (paper II). Since female gender was not an independent risk factor in a multivariate analysis in neither ours nor other reports, the risk appears to be related to other factors rather than gender per se. [5, 13, 68, 73, 74, 114, 117] The risk of subsequent amputation in relation to diabetes and old age are well documented. [7, 64, 100, 107, 113, 117, 124, 156, 161] This should however not be interpreted as a reason for avoiding surgical treatment of diabetic or elderly patients. Cost benefit analysis and quality of life aspects supports the view that vascular intervention should be attempted also for diabetic as well as elderly patients, since the alternative to intervention often is primary amputation. [100, 136, 159, 160, 164, 165]

Our Stockholm study showed that old age was strongly associated with risk of amputation (paper II). It is not clear why age is so strongly related to this risk, but it is reasonable to believe that a larger number of elderly suffer from infrainguinal disease and diabetes. Anatomical conditions, such as the elderly having a lack of patent outflow vessels distally, thus excluding further interventions also increases the risk of secondary amputations.

The Stockholm study shows that many elderly patients treated with embolectomy were amputated and women more frequently than men (paper II). This can be explained by women's longevity or that more women with "acute on chronic" ischemia were treated with embolectomy rather than with adequate treatment for their thrombosis.

A higher number of amputated patients were treated with infrainguinal interventions compared to suprainguinal interventions in our Stockholm study (paper II). The amputation risk among our CLI patients, in the matched subgroup and in a regression model, was however not influenced by localisation of treated lesions (paper III). This can be interpreted as if the risk for amputation depends on the previously described varying distribution of risk factors between the groups, rather than the localisation of lesions. The lack of influence on the risk for amputation among CLI patients may be due to the fact that patients classified as "suprainguinal" actually suffer from multilevel disease. They therefore probably have the same basic characteristics as patients with infrainguinal disease.

Acute ischemia

Others have also reported an overall reduction of the number of embolectomies during the last decades. [137, 166] This can partly be explained by an increased knowledge among surgeons in differentiating between acute and "acute on chronic" ischemia. [137, 166] The unchanged number of women treated with embolectomy during the observed period may reflect a true higher incidence of embolic events in women compared to men. This can be related to the higher number of women in the older age groups. It may also be explained by an underestimate of existing chronic ischemia in women compared to men, which would mistakenly lead surgeons to embolectomise women with a thrombosis, rather than treat them with more appropriate methods. Table 5. This would explain the higher amputation and mortality rate in embolectomised women compared to that for men.

The decline in the number of all patients treated for acute ischemia may be related to a decreasing incidence of embolic events and better pro-fylaxis. Thrombolytic therapy can not be identified in this material but can contribute to the decline in the number of embolectomies.

The future

In these investigations we have described some of the specific conditions for women treated with vascular interventions for LLI. This thesis illustrated the fact that, despite our present knowledge in this field many questions still remain unanswered.

Today a majority of patients treated are women. It is important to investigate if there are specific conditions present in women affecting the development of disease, and if so, if such conditions are modifiable or treatable. It is likely that the number of women requiring intervention will increase even further, considering the changing smoking habits of women and men.
The true prevalence rate of LLI in women and men is unknown. It is necessary to increase our knowledge about prevalence rates, associated risk factors, progression of disease and number of treated patients from a gender perspective as well as selection and referral patterns. Such knowledge would also increase our ability to improve primary and secondary prevention for these patients, and to identify if there are gender differences in this respect and whether such differences are justified. There is an ongoing debate whether gender differences in secondary prevention of CHD exist. [167, 168]

It is important to describe any changes in vascular interventions that occurred after 1994, since significant changes in patient characteristics and interventional techniques are likely to have arisen.

The interest in pharmacological or non-interventional treatment of this patient group is growing and is a field where gender aspects play a vital role. To include women in clinical trials and analyse outcome in women and men separately, as is the case for diabetic and non diabetic patients, will be crucial for our ability to use any new drugs in clinical practice for both women and men.

Obvious biological differences do exist between women and men. The best evidence for this in our patient group, is the age difference between treated women and men. A torrent of reports has been published, investigating the direct effects of oestrogen on haemostasis, coagulation, inflammation, angiogenesis and vessel wall interactions. Almost all these reports generate their hypothesis from the general standpoint that oestrogen protects women against CHD. Even basic knowledge about the effect of oestrogen is still lacking and the results from clinical trials are contradictory. The effect of oestrogen on peripheral arteries is an extremely neglected area of research.

It is not evident that arteriosclerotic disease in the coronary and carotid vessels is identical to that of other peripheral vessels. This needs further studies, and the gender perspective in this field can be important. Can the findings in our report concerning reproductive history be explained by differences in these vessels, for example a different susceptibility to oestrogen and smoking? Basic characteristics have been described to differ in patients with suprainguinal disease compared to patients with infrainguinal disease Figure 1. In order to enhance our knowledge of these two quite different patient groups, we should investigate if possible differences in the pathogenesis of arteriosclerotic disease at these locations can be found.

The possibility that women may have a different inflammatory response compared to men has been reported in CHD patients. [169, 170] It has as far as we know not at all been explored for peripheral arteries in women, only in men . The strong relationship between autoimmune disease and CHD, the higher CMV titers in women compared to men as predictors for CHD are all findings that indicate that arteriosclerotic disease in some women can be different from that described in men. [169, 170, 172] Hyperhomocysteinemia is a factor that has been reported to increase the risk for LLI in young women, the clinical implications of this are today unclear. [173] In the two other large patient groups treated by vascular surgeons, abdominal aortic aneurysms and carotid arteriosclerosis, there is also insufficient knowledge about special conditions affecting women. Interesting future studies should focus on: gender differences in preoperative conditions, true prevalence rates, the need for different diagnostic criteria, differences in pathogenesis for women and men, the influence of oestrogen levels and other risk factors on the progression of disease as well as factors influencing poorer outcome for women and the development of new endovascular devices more suitable for the treatment of aneurysms in women.

SUMMARY AND CONCLUSIONS

I. A growing proportion of patients treated for LLI are women. The localisation of the treated lesions are distributed similarly in women and men.

II. Women have similar amputation rates and better survival than men after vascular interventions for LLI. Survival and amputation rates are strongly related to increasing age.

III. Apart from old age, women treated for CLI have similar or better pre-operative conditions than men. A high proportion of women were treated for suprainguinal disease compared to men. Again, outcome was similar between the sexes.

IV. Reproductive history in women treated for LLI is similar to that of women in the general population.

The number of vascular interventions, especially in women, have probably increased further after the observed period, and the increase can be expected to continue. Biological and anatomical differences can probably explain several of the found differences between the sexes, such as localisation of treated lesions and age.

Provided there is a gender bias in selection for interventions, a need for education for patients and physicians about LLI seems necessary.

The similar outcome between women and men indicates that we should continue to focus on established risk factors in our preoperative evaluation, rather than gender or reproductive history in women.

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REFERENCES

1. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. Jama 2001;286(11):1317-24.
2. Cheng KS, Baker CR, Hamilton G, Hoeks AP, Seifalian AM. Arterial elastic properties and cardiovascular risk/event. Eur J Vasc Endovasc Surg 2002;24(5):383-97.
3. Plante GE. Impact of aging on the body's vascular system. Metabolism 2003;52(10 Suppl 2):31-5.
4. Melliere D, Berrahal D, Desgranges P, Allaire E, Becquemin JP, Perlemuter L, et al. Influence of diabetes on revascularisation procedures of the aorta and lower limb arteries: early results. Eur J Vasc Endovasc Surg 1999;17(5):438-41.
5. Frangos SG, Karimi S, Kerstein MD, Harpavat M, Sumpio B, Roberts AB, et al. Gender does not impact infrainguinal vein bypass graft outcome. Surgery 2000;127(6):679-86.
6. Enzler MA, Ruoss M. Does female sex adversely affect long-term patency of peripheral arterial reconstructions? [letter; comment]. J Vasc Surg 1994;19(6):1098.
7. Eugster T, Gurke L, Obeid T, Stierli P. Infrainguinal arterial reconstruction: female gender as risk factor for outcome. Eur J Vasc Endovasc Surg 2002;24(3):245-8.
8. Cheng SW, Ting AC, Lau H, Wong J. Survival in patients with chronic lower extremity ischemia: a risk factor analysis. Ann Vasc Surg 2000;14(2):158-65.
9. Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. Circulation 1995;91(5):1472-9.
10. Kannel WB, McGee DL. Update on some epidemiologic features of intermittent claudication: the Framingham Study. J Am Geriatr Soc 1985;33(1):13-8.
11. Brismar K. Diabetes and cardiovascular disease in women. In: Schenck-Gustafsson K, editor. Cardiovascular disease in women. Lund, Sweden: Studentlitteratur; 2003.
12. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendic S, Ryden L, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. Lancet 2002;359(9324):2140-4.
13. Magnant JG, Cronenwett JL, Walsh DB, Schneider JR, Besso SR, Zwolak RM. Surgical treatment of infrainguinal arterial occlusive disease in women. J Vasc Surg 1993;17(1):67-76; discussion 76-8.
14. Enzler MA, Ruoss M, Seifert B, Berger M. The influence of gender on the outcome of arterial procedures in the lower extremity. Eur J Vasc Endovasc Surg 1996;11(4):446-52.
15. Fowkes FG, Dunbar JT, Lee AJ. Risk factor profile of nonsmokers with peripheral arterial disease. Angiology 1995;46(8):657-62.
16. Sonesson B, Ahlgren AR, Lazer L, Lanne T. Does long-term smoking affect aortic stiffness more in women than in men? Clin Physiol 1997;17(5):439-47.
17. Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. Eur Heart J 1999;20(5):344-53.
18. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. Maturitas 1992;14(2):103-15.
19. Rodstrom K, Bengtsson C, Milsom I, Lissner L, Sundh V, Bjourkelund C. Evidence for a secular trend in menopausal age: a population study of women in Gothenburg. Menopause 2003;10(6):538-43.

20. Cramer DW, Xu H. Predicting age at menopause. Maturitas 1996;23(3):319-26.
21. Gariepy J, Denarie N, Chironi G, Salomon J, Levenson J, Simon A. Gender difference in the influence of smoking on arterial wall thickness. Atherosclerosis 2000;153(1):139-45.
22. Stensland-Bugge E, Bonaa KH, Joakimsen O, Njolstad I. Sex differences in the relationship of risk factors to subclinical carotid atherosclerosis measured 15 years later : the Tromso study. Stroke 2000;31(3):574-81.
23. Schenk-Gustafsson K. The female heart - cardiovascular disease in women. Lund, Sweden: Studentlitteratur; 2003.
24. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344(8934):1383-9.
25. Volterrani M, Rosano G, Coats A, Beale C, Collins P. Estrogen acutely increases peripheral blood flow in postmenopausal women. Am J Med 1995;99(2):119-22.
26. Lieberman EH, Gerhard MD, Uehata A, Walsh BW, Selwyn AP, Ganz P, et al. Estrogen improves endothelium-dependent, flow-mediated vasodilation in postmenopausal women. Ann Intern Med 1994;121(12):936-41.
27. Williams JK, Anthony MS, Honore EK, Herrington DM, Morgan TM, Register TC, et al. Regression of atherosclerosis in female monkeys. Arterioscler Thromb Vasc Biol 1995;15(7):827-36.
28. Tuck CH, Holleran S, Berglund L. Hormonal regulation of lipoprotein(a) levels: effects of estrogen replacement therapy on lipoprotein(a) and acute phase reactants in postmenopausal women. Arterioscler Thromb Vasc Biol 1997;17(9):1822-9.
29. Piercy KT, Donnell RL, Kirkpatrick SS, Timaran CH, Stevens SL, Freeman MB, et al. Effects of estrogen, progesterone, and combination exposure on interleukin-1 beta-induced expression of VCAM-1, ICAM-1, PECAM, and E-selectin by human female iliac artery endothelial cells. J Surg Res 2002;105(2):215-9.
30. Gilligan DM, Badar DM, Panza JA, Quyyumi AA, Cannon RO, 3rd. Acute vascular effects of estrogen in postmenopausal women. Circulation 1994;90(2):786-91.
31. Adams MR, Kaplan JR, Manuck SB, Koritnik DR, Parks JS, Wolfe MS, et al. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized monkeys. Lack of an effect of added progesterone. Arteriosclerosis 1990;10(6):1051-7.
32. Barrett-Connor E, Slone S, Greendale G, Kritz-Silverstein D, Espeland M, Johnson SR, et al. The Postmenopausal Estrogen/Progestin Interventions Study: primary outcomes in adherent women. Maturitas 1997;27(3):261-74.
33. Kyriakides ZS, Petinakis P, Kaklamanis L, Sbarouni E, Karayannakos P, Iliopoulos D, et al. Intramuscular administration of estrogen may promote angiogenesis and perfusion in a rabbit model of chronic limb ischemia. Cardiovasc Res 2001;49(3):626-33.
34. Chilvers CE, Knibb RC, Armstrong SJ, Woods KL, Logan RF. Post menopausal hormone replacement therapy and risk of acute myocardial infarction—a case control study of women in the East Midlands, UK. Eur Heart J 2003;24(24):2197-205.
35. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). Jama 2002;288(1):49-57.
36. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349(6):523-34.
37. Joakimsen O, Bonaa KH, Stensland-Bugge E, Jacobsen BK. Population-based study of age at menopause and ultrasound assessed carotid atherosclerosis: The Tromso Study. J Clin Epidemiol 2000;53(5):525-30.
38. Jacobsen BK, Nilssen S, Heuch I, Kvale G. Does age at natural menopause affect mortality from ischemic heart disease? J Clin Epidemiol 1997;50(4):475-9.

39. Cooper GS, Ephross SA, Weinberg CR, Baird DD, Whelan EA, Sandler DP. Menstrual and reproductive risk factors for ischemic heart disease. Epidemiology 1999;10(3):255-9.
40. Falkeborn M, Schairer C, Naessen T, Persson I. Risk of myocardial infarction after oophorectomy and hysterectomy. J Clin Epidemiol 2000;53(8):832-7.
41. Palmer JR, Rosenberg L, Shapiro S. Reproductive factors and risk of myocardial infarction. Am J Epidemiol 1992;136(4):408-16.
42. van der Schouw YT, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. Lancet 1996;347(9003):714-8.
43. Hu FB, Grodstein F, Hennekens CH, Colditz GA, Johnson M, Manson JE, et al. Age at natural menopause and risk of cardiovascular disease. Arch Intern Med 1999;159(10):1061-6.
44. Cronenwett JL, Davis JT, Jr., Gooch JB, Garrett HE. Aortoiliac occlusive disease in women. Surgery 1980;88(6):775-84.
45. Weiss NS. Premature menopause and aortoiliac occlusive disease. J Chronic Dis 1972;25(3):133-8.
46. de Kleijn MJ, van der Schouw YT, van der Graaf Y. Reproductive history and cardiovascular disease risk in postmenopausal women: a review of the literature. Maturitas 1999;33(1):7-36.
47. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. A prospective study of age at menarche, parity, age at first birth, and coronary heart disease in women. Am J Epidemiol 1987;126(5):861-70.
48. Ness RB, Harris T, Cobb J, Flegal KM, Kelsey JL, Balanger A, et al. Number of pregnancies and the subsequent risk of cardiovascular disease. N Engl J Med 1993;328(21):1528-33.
49. Humphries KH, Westendorp IC, Bots ML, Spinelli JJ, Carere RG, Hofman A, et al. Parity and carotid artery atherosclerosis in elderly women: The Rotterdam Study. Stroke 2001;32(10):2259-64.
50. Sidney S, Siscovick DS, Petitti DB, Schwartz SM, Quesenberry CP, Psaty BM, et al. Myocardial infarction and use of low-dose oral contraceptives: a pooled analysis of 2 US studies. Circulation 1998;98(11):1058-63.
51. Beral V, Hermon C, Kay C, Hannaford P, Darby S, Reeves G. Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study. Bmj 1999;318(7176):96-100.
52. Burkman RT, Collins JA, Greene RA. Current perspectives on benefits and risks of hormone replacement therapy. Am J Obstet Gynecol 2001;185(2 Suppl):S13-23.
53. WHO. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet 1997;349(9060):1202-9.
54. Tanis BC, van den Bosch MA, Kemmeren JM, Cats VM, Helmerhorst FM, Algra A, et al. Oral contraceptives and the risk of myocardial infarction. N Engl J Med 2001;345(25):1787-93.
55. Mosca L, Collins P, Herrington DM, Mendelsohn ME, Pasternak RC, Robertson RM, et al. Hormone replacement therapy and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 2001;104(4):499-503.
56. Hsia J, Simon JA, Lin F, Applegate WB, Vogt MT, Hunninghake D, et al. Peripheral arterial disease in randomized trial of estrogen with progestin in women with coronary heart disease: the Heart and Estrogen/Progestin Replacement Study. Circulation 2000;102(18):2228-32.
57. Westendorp IC, in't Veld BA, Grobbee DE, Pols HA, Meijer WT, Hofman A, et al. Hormone replacement therapy and peripheral arterial disease: the Rotterdam study. Arch Intern Med 2000;160(16):2498-502.
58. Yeh ST, Morton DJ, Barrett-Connor E. Lower extremity arterial disease in older women: the Rancho Bernardo Study. J Womens Health Gend Based Med 2000;9(4):373-80.

59. Nabulsi AA, Folsom AR, Szklo M, White A, Higgins M, Heiss G. No association of menopause and hormone replacement therapy with carotid artery intima-media thickness. Atherosclerosis Risk in Communities (ARIC) Study Investigators. Circulation 1996;94(8):1857-63.
60. Akkad A, Hartshorne T, Bell PR, al-Azzawi F. Carotid plaque regression on oestrogen replacement: a pilot study. Eur J Vasc Endovasc Surg 1996;11(3):347-8.
61. Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. Jama 2003;289(20):2673-84.
62. Viscoli CM, Brass LM, Kernan WN, Sarrel PM, Suissa S, Horwitz RI. A clinical trial of estrogen-replacement therapy after ischemic stroke. N Engl J Med 2001;345(17):1243-9.
63. TASC. Management of Peripheral Arterial Disease (PAD). In: TransAtlantic Inter-Society Consensus; 1999.
64. Dormandy J, Heeck L, Vig S. The fate of patients with critical leg ischemia. Semin Vasc Surg 1999;12(2):142-7.
65. Hooi JD, Stoffers HE, Kester AD, Rinkens PE, Kaiser V, van Ree JW, et al. Risk factors and cardiovascular diseases associated with asymptomatic peripheral arterial occlusive disease. The Limburg PAOD Study. Peripheral Arterial Occlusive Disease. Scand J Prim Health Care 1998;16(3):177-82.
66. Leng GC, Lee AJ, Fowkes FG, Whiteman M, Dunbar J, Housley E, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. Int J Epidemiol 1996;25(6):1172-81.
67. Cacoub P, Godeau P. Risk factors for atherosclerotic aortoiliac occlusive disease. Ann Vasc Surg 1993;7(4):394-405.
68. AhChong AK, Chiu KM, Wong M, Yip AW. The influence of gender difference on the outcomes of infrainguinal bypass for critical limb ischaemia in Chinese patients. Eur J Vasc Endovasc Surg 2002;23(2):134-9.
69. Hultgren R, Sjogren B, Soderberg M, Takolander R, Wahlberg E, Wahlberg M, et al. Sexual function in women suffering from aortoiliac occlusive disease. Eur J Vasc Endovasc Surg 1999;17(4):306-12.
70. Cronenwett JL. Infrainguinal occlusive disease. Semin Vasc Surg 1995;8(4):284-8.
71. Nevelsteen A, Wouters L, Suy R. Aortofemoral dacron reconstruction for aorto-iliac occlusive disease: a 25-year survey. Eur J Vasc Surg 1991;5(2):179-86.
72. Schneider JR. Aortoiliac occlusive disease. Semin Vasc Surg 1995;8(4):277-83.
73. Roddy SP, Darling RC, 3rd, Maharaj D, Chang BB, Paty PS, Kreienberg PB, et al. Gender-related differences in outcome: an analysis of 5880 infrainguinal arterial reconstructions. J Vasc Surg 2003;37(2):399-402.
74. Harris EJ, Jr., Taylor LM, Jr., Moneta GL, Porter JM. Outcome of infrainguinal arterial reconstruction in women [see comments]. J Vasc Surg 1993;18(4):627-34; discussion 634-6.
75. Hiatt WR, Nehler MR. Peripheral arterial disease. Adv Intern Med 2001;47:89-110.
76. Tangelder MJ, Algra A, Lawson JA, Eikelboom BC. Risk factors for occlusion of infrainguinal bypass grafts. Eur J Vasc Endovasc Surg 2000;20(2):118-24.
77. Jensen SA, Vatten LJ, Romundstad PR, Myhre HO. The prevalence of intermittent claudication. Sex-related differences have been eliminated. Eur J Vasc Endovasc Surg 2003;25(3):209-12.
78. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 1991;20(2):384-92.
79. Skau T, Jonsson B. Prevalence of symptomatic leg ischaemia in a Swedish community—an epidemiological study. Eur J Vasc Surg 1993;7(4):432-7.

80. Stoffers HE, Rinkens PE, Kester AD, Kaiser V, Knottnerus JA. The prevalence of asymptomatic and unrecognized peripheral arterial occlusive disease. Int J Epidemiol 1996;25(2):282-90.
81. Hooi JD, Stoffers HE, Knottnerus JA, van Ree JW. The prognosis of non-critical limb ischaemia: a systematic review of population-based evidence. Br J Gen Pract 1999;49(438):49-55.
82. Muluk SC, Muluk VS, Kelley ME, Whittle JC, Tierney JA, Webster MW, et al. Outcome events in patients with claudication: a 15-year study in 2777 patients. J Vasc Surg 2001;33(2):251-7; discussion 257-8.
83. Aquino R, Johnnides C, Makaroun M, Whittle JC, Muluk VS, Kelley ME, et al. Natural history of claudication: long-term serial follow-up study of 1244 claudicants. J Vasc Surg 2001;34(6):962-70.
84. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326(6):381-6.
85. Lepantalo M, Matzke S. Outcome of unreconstructed chronic critical leg ischaemia. Eur J Vasc Endovasc Surg 1996;11(2):153-7.
86. Beischer W, Dembski JC, Gruss JD, Hofgartner F, Horsch A, Horsch S, et al. Low-dose iloprost infusions compared to the standard dose in patients with peripheral arterial occlusive disease Fontaine stage IV. DAWID Study Group. Vasa 1998;27(1):15-9.
87. Jonason T, Bergstrom R. Cessation of smoking in patients with intermittent claudication. Effects on the risk of peripheral vascular complications, myocardial infarction and mortality. Acta Med Scand 1987;221(3):253-60.
88. Chong PF, Golledge J, Greenhalgh RM, Davies AH. Exercise therapy or angioplasty? A summation analysis. Eur J Vasc Endovasc Surg 2000;20(1):4-12.
89. Tan KH, Cotterrell D, Sykes K, Sissons GR, de Cossart L, Edwards PR. Exercise training for claudicants: changes in blood flow, cardiorespiratory status, metabolic functions, blood rheology and lipid profile. Eur J Vasc Endovasc Surg 2000;20(1):72-8.
90. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. N Engl J Med 2002;347(24):1941-51.
91. Kugler CF, Rudofsky G. The challenges of treating peripheral arterial disease. Vasc Med 2003;8(2):109-14.
92. Treat-Jacobson D, Walsh ME. Treating patients with peripheral arterial disease and claudication. J Vasc Nurs 2003;21(1):5-14; quiz 15-6.
93. Dawson DL, Cutler BS, Hiatt WR, Hobson RW, 2nd, Martin JD, Bortey EB, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. Am J Med 2000;109(7):523-30.
94. Hiatt WR. Pharmacologic therapy for peripheral arterial disease and claudication. J Vasc Surg 2002;36(6):1283-91.
95. Bradbury AW, Bell J, Lee AJ, Prescott RJ, Gillespie I, Stansby G, et al. Bypass or angioplasty for severe limb ischaemia? A Delphi Consensus Study. Eur J Vasc Endovasc Surg 2002;24(5):411-6.
96. Tunis SR, Bass EB, Steinberg EP. The use of angioplasty, bypass surgery, and amputation in the management of peripheral vascular disease [see comments]. N Engl J Med 1991;325(8):556-62.
97. Sayers RD, Thompson MM, Varty K, Jagger C, Bell PR. Changing trends in the management of lower-limb ischaemia: a 17-year review. Br J Surg 1993;80(10):1269-73.
98. Ebskov LB, Schroeder TV, Holstein PE. Epidemiology of leg amputation: the influence of vascular surgery. Br J Surg 1994;81(11):1600-3.
99. Lepantalo M, Salenius JP, Harjola PT. Trends in vascular surgery—an evaluation of operative activity in Finland 1976-1992. Ann Chir Gynaecol 1996;85(3):225-9.

100. Hallett JW, Jr., Byrne J, Gayari MM, Ilstrup DM, Jacobsen SJ, Gray DT. Impact of arterial surgery and balloon angioplasty on amputation: a population-based study of 1155 procedures between 1973 and 1992 [see comments]. J Vasc Surg 1997;25(1):29-38.
101. Mattes E, Norman PE, Jamrozik K. Falling incidence of amputations for peripheral occlusive arterial disease in Western Australia between 1980 and 1992. Eur J Vasc Endovasc Surg 1997;13(1):14-22.
102. Pell JP, Whyman MR, Fowkes FG, Gillespie I, Ruckley CV. Trends in vascular surgery since the introduction of percutaneous transluminal angioplasty. Br J Surg 1994;81(6):832-5.
103. Luther M, Kantonen I, Lepantalo M, Salenius J, Group KY. Arterial intervention and reduction in amputation for chronic critical leg ischaemia. Br J Surg 2000;87(4):454-8.
104. Karlstrom L, Bergqvist D. Effects of vascular surgery on amputation rates and mortality. Eur J Vasc Endovasc Surg 1997;14(4):273-83.
105. Nasr MK, McCarthy RJ, Hardman J, Chalmers A, Horrocks M. The increasing role of percutaneous transluminal angioplasty in the primary management of critical limb ischaemia. Eur J Vasc Endovasc Surg 2002;23(5):398-403.
106. Molloy KJ, Nasim A, London NJ, Naylor AR, Bell PR, Fishwick G, et al. Percutaneous transluminal angioplasty in the treatment of critical limb ischemia. J Endovasc Ther 2003;10(2):298-303.
107. Gutteridge W, Torrie EP, Galland RB. Cumulative risk of bypass, amputation or death following percutaneous transluminal angioplasty. Eur J Vasc Endovasc Surg 1997;14(2):134-9.
108. Petticrew M, McKee M, Jones J. Coronary artery surgery: are women discriminated against? Bmj 1993;306(6886):1164-6.
109. Loop FD, Golding LR, MacMillan JP, Cosgrove DM, Lytle BW, Sheldon WC. Coronary artery surgery in women compared with men: analyses of risks and long-term results. J Am Coll Cardiol 1983;1(2 Pt 1):383-90.
110. Khan SS, Matloff JM. Surgical revascularization in women. Curr Opin Cardiol 1991;6(6):904-11.
111. Steingart RM, Packer M, Hamm P, Coglianese ME, Gersh B, Geltman EM, et al. Sex differences in the management of coronary artery disease. Survival and Ventricular Enlargement Investigators. N Engl J Med 1991;325(4):226-30.
112. Pell JP, Walsh D, Norrie J, Berg G, Colquhoun AD, Davidson K, et al. Outcomes following coronary artery bypass grafting and percutaneous transluminal coronary angioplasty in the stent era: a prospective study of all 9890 consecutive patients operated on in Scotland over a two year period. Heart 2001;85(6):662-6.
113. Bertele V, Roncaglioni MC, Pangrazzi J, Terzian E, Tognoni EG. Clinical outcome and its predictors in 1560 patients with critical leg ischaemia. Chronic Critical Leg Ischaemia Group. Eur J Vasc Endovasc Surg 1999;18(5):401-10.
114. Mays BW, Towne JB, Fitzpatrick CM, Smart SC, Cambria RA, Seabrook GR, et al. Women have increased risk of perioperative myocardial infarction and higher long-term mortality rates after lower extremity arterial bypass grafting. J Vasc Surg 1999;29(5):807-12; discussion 812-3.
115. Luther M, Lepantalo M. Femorotibial reconstructions for chronic critical leg ischaemia: influence on outcome by diabetes, gender and age. Eur J Vasc Endovasc Surg 1997;13(6):569-77.
116. Conte MS, Belkin M, Upchurch GR, Mannick JA, Whittemore AD, Donaldson MC. Impact of increasing comorbidity on infrainguinal reconstruction: a 20-year perspective. Ann Surg 2001;233(3):445-52.
117. Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Outcome of revascularization procedures for peripheral arterial occlusive disease in Ontario between 1991 and 1998: a population-based study. J Vasc Surg 2003;38(2):279-88.

118. Watson HR, Schroeder TV, Simms MH, Horrocks M. Association of sex with patency of femorodistal bypass grafts. Eur J Vasc Endovasc Surg 2000;20(1):61-6.
119. Nicoloff AD, Taylor LM, Jr., McLafferty RB, Moneta GL, Porter JM. Patient recovery after infrainguinal bypass grafting for limb salvage. J Vasc Surg 1998;27(2):256-63; discussion 264-6.
120. Kalra M, Gloviczki P, Bower TC, Panneton JM, Harmsen WS, Jenkins GD, et al. Limb salvage after successful pedal bypass grafting is associated with improved long-term survival. J Vasc Surg 2001;33(1):6-16.
121. Allen BT, Rubin BG, Reilly JM, Thompson RW, Anderson CB, Flye MW, et al. Limb salvage and patency after aortic reconstruction in younger patients. Am J Surg 1995;170(2):188-92.
122. Timaran CH, Stevens SL, Freeman MB, Goldman MH. Predictors for adverse outcome after iliac angioplasty and stenting for limb-threatening ischemia. J Vasc Surg 2002;36(3):507-13.
123. Tarry WC, Walsh DB, Birkmeyer NJ, Fillinger MF, Zwolak RM, Cronenwett JL. Fate of the contralateral leg after infrainguinal bypass. J Vasc Surg 1998;27(6):1039-47; discussion 1047-8.
124. Tunis SR, Bass EB, Klag MJ, Steinberg EP. Variation in utilization of procedures for treatment of peripheral arterial disease. A look at patient characteristics. Arch Intern Med 1993;153(8):991-8.
125. Jamsen TS, Manninen HI, Jaakkola PA, Matsi PJ. Long-term outcome of patients with claudication after balloon angioplasty of the femoropopliteal arteries. Radiology 2002;225(2):345-52.
126. Jamsen T, Manninen H, Tulla H, Matsi P. The final outcome of primary infrainguinal percutaneous transluminal angioplasty in 100 consecutive patients with chronic critical limb ischemia. J Vasc Interv Radiol 2002;13(5):455-63.
127. Nasr MK, McCarthy RJ, Budd JS, Horrocks M. Infrainguinal bypass graft patency and limb salvage rates in critical limb ischemia: influence of the mode of presentation. Ann Vasc Surg 2003;17(2):192-7.
128. Watson HR, Buth J, Schroeder TV, Simms MH, Horrocks M. Incidence of stenoses in femorodistal bypass vein grafts in a multicentre study. Eur J Vasc Endovasc Surg 2000;20(1):67-71.
129. Timaran CH, Stevens SL, Grandas OH, Freeman MB, Goldman MH. Influence of hormone replacement therapy on the outcome of iliac angioplasty and stenting. J Vasc Surg 2001;33(2 Suppl):S85-92.
130. Timaran CH, Stevens SL, Grandas OH, Piercy KT, Freeman MB, Goldman MH. Influence of hormone replacement therapy on graft patency after femoropopliteal bypass grafting. J Vasc Surg 2000;32(3):506-16; 516-8.
131. Klevsgard R, Risberg BO, Thomsen MB, Hallberg IR. A 1-year follow-up quality of life study after hemodynamically successful or unsuccessful surgical revascularization of lower limb ischemia. J Vasc Surg 2001;33(1):114-22.
132. Cassar K, Bachoo P, Brittenden J. The effect of peripheral percutaneous transluminal angioplasty on quality of life in patients with intermittent claudication. Eur J Vasc Endovasc Surg 2003;26(2):130-6.
133. de Kleijn MJ, Bots ML, Bak AA, Westendorp IC, Planellas J, Coelingh Bennink HJ, et al. Hormone replacement therapy in perimenopausal women and 2-year change of carotid intima-media thickness. Maturitas 1999;32(3):195-204.
134. Ouriel K, Green RM, Waldman D, Greenberg RK, Shortell CK, Illig K. A model for merging vascular surgery and interventional radiology: clinical and economical implications. J Vasc Surg 1998;28(6):1006-10; discussion 1011-3.
135. Green RM, Waldman D. Five-year results of a merger between vascular surgeons and interventional radiologists in a university medical center. J Vasc Surg 2003;38(6):1213-9.
136. Earnshaw JJ, Hayward JK, Horrocks M, Baird RN. The importance of vascular surgical audit to surgeons, patients and purchasers. Eur J Vasc Surg 1992;6(5):540-4.

137. Jivegard L, Wingren U. Management of acute limb ischaemia over two decades: the Swedish experience. Eur J Vasc Endovasc Surg 1999;18(2):93-5.
138. Kroger K, Suckel A, Hirche H, Rudofsky G. Different prevalence of asymptomatic atherosclerotic lesions in males and females. Vasc Med 1999;4(2):61-5.
139. Baker L, Meldrum KK, Wang M, Sankula R, Vanam R, Raiesdana A, et al. The role of estrogen in cardiovascular disease. J Surg Res 2003;115(2):325-44.
140. Jacobsen BK, Knutsen SF, Fraser GE. Age at natural menopause and total mortality and mortality from ischemic heart disease: the Adventist Health Study. J Clin Epidemiol 1999;52(4):303-7.
141. John S, Jacobi J, Schlaich MP, Delles C, Schmieder RE. Effects of oral contraceptives on vascular endothelium in premenopausal women. Am J Obstet Gynecol 2000;183(1):28-33.
142. Bellinger DA, Williams JK, Adams MR, Honore EK, Bender DE. Oral contraceptives and hormone replacement therapy do not increase the incidence of arterial thrombosis in a nonhuman primate model. Arterioscler Thromb Vasc Biol 1998;18(1):92-9.
143. Van Den Bosch MA, Kemmeren JM, Tanis BC, Mali WP, Helmerhorst FM, Rosendaal FR, et al. The RATIO study: oral contraceptives and the risk of peripheral arterial disease in young women. J Thromb Haemost 2003;1(3):439-44.
144. WHO. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet 1996;348(9026):498-505.
145. Smith FB, Lee AJ, Hau CM, Rumley A, Lowe GD, Fowkes FG. Plasma fibrinogen, haemostatic factors and prediction of peripheral arterial disease in the Edinburgh Artery Study. Blood Coagul Fibrinolysis 2000;11(1):43-50.
146. NBHW Nbohaw. Monitoring public health and social conditions in Sweden 1992–2002: NBHW; 2001.
147. Nilsson S, Carstensen JM, Pershagen G. Mortality among male and female smokers in Sweden: a 33 year follow up. J Epidemiol Community Health 2001;55(11):825-30.
148. McLafferty RB, Dunnington GL, Mattos MA, Markwell SJ, Ramsey DE, Henretta JP, et al. Factors affecting the diagnosis of peripheral vascular disease before vascular surgery referral. J Vasc Surg 2000;31(5):870-9.
149. Evans SM, Adam DJ, Bradbury AW. The influence of gender on outcome after ruptured abdominal aortic aneurysm. J Vasc Surg 2000;32(2):258-62.
150. Semmens JB, Norman PE, Lawrence-Brown MM, Holman CD. Influence of gender on outcome from ruptured abdominal aortic aneurysm. Br J Surg 2000;87(2):191-4.
151. Wamala SP, Lynch J, Kaplan GA. Women's exposure to early and later life socioeconomic disadvantage and coronary heart disease risk: the Stockholm Female Coronary Risk Study. Int J Epidemiol 2001;30(2):275-84.
152. Bergqvist D, Troeng T. [Vascular surgery is steadily increasing in Sweden]. Lakartidningen 1998;95(25):2940-3.
153. Al-Omran M, Tu JV, Johnston KW, Mamdani MM, Kucey DS. Use of interventional procedures for peripheral arterial occlusive disease in Ontario between 1991 and 1998: a population-based study. J Vasc Surg 2003;38(2):289-95.
154. Plecha EJ, Freischlag JA, Seabrook GR, Towne JB. Femoropopliteal bypass revisited: an analysis of 138 cases. Cardiovasc Surg 1996;4(2):195-9.
155. van den Akker PJ, van Schilfgaarde R, Brand R, van Bockel JH, Terpstra JL. Aortoiliac and aortofemoral reconstruction of obstructive disease. Am J Surg 1994;167(4):379-85.
156. Mlekusch W, Schillinger M, Sabeti S, Maca T, Ahmadi R, Minar E. Clinical outcome and prognostic factors for ischaemic ulcers treated with PTA in lower limbs. Eur J Vasc Endovasc Surg 2002;24(2):176-81.

157. Matsagas MI, Rivera MA, Tran T, Mitchell A, Robless P, Davies AH, et al. Clinical Outcome Following Infra-Inguinal Percutaneous Transluminal Angioplasy for Critical Limb Ischemia. Cardiovasc Intervent Radiol 2003;26(2).
158. Lofberg AM, Karacagil S, Ljungman C, Westman B, Bostrom A, Hellberg A, et al. Percutaneous transluminal angioplasty of the femoropopliteal arteries in limbs with chronic critical lower limb ischemia. J Vasc Surg 2001;34(1):114-21.
159. Chang JB, Stein TA. Infrainguinal revascularizations in octogenarians and septuagenarians. J Vasc Surg 2001;34(1):133-8.
160. Eskelinen E, Luther M, Eskelinen A, Lepantalo M. Infrapopliteal bypass reduces amputation incidence in elderly patients: a population-based study. Eur J Vasc Endovasc Surg 2003;26(1):65-8.
161. Veith FJ, Gupta SK, Wengerter KR, Goldsmith J, Rivers SP, Bakal CW, et al. Changing arteriosclerotic disease patterns and management strategies in lower-limb-threatening ischemia. Ann Surg 1990;212(4):402-12; discussion 412-4.
162. Wahlberg E, Lepner U, Olofsson P. Limb loss in association with vascular surgery—a five-year series of major lower-limb amputation. Eur J Surg 1994;160(10):561-7.
163. Powell RJ, Fillinger M, Walsh DB, Zwolak R, Cronenwett JL. Predicting outcome of angioplasty and selective stenting of multisegment iliac artery occlusive disease. J Vasc Surg 2000;32(3):564-9.
164. Choi D, Darling RC, 3rd, Roddy SP, Chang BB, Lloyd WE, Paty PS, et al. Infrainguinal reconstruction in octogenarians: should age be a contraindication? Ann Vasc Surg 2000;14(1):67-72.
165. Gahtan V, Harpavat M, Roberts AB, Kerstein MD. Impact of diabetes mellitus on infrainguinal bypass grafting. J Diabetes Complications 1998;12(4):197-200.
166. Eliason JL, Wainess RM, Proctor MC, Dimick JB, Cowan JA, Jr., Upchurch GR, Jr., et al. A national and single institutional experience in the contemporary treatment of acute lower extremity ischemia. Ann Surg 2003;238(3):382-9; discussion 389-90.
167. Hippisley-Cox J, Pringle M, Crown N, Meal A, Wynn A. Sex inequalities in ischaemic heart disease in general practice: cross sectional survey. Bmj 2001;322(7290):832.
168. Nilsson P, Brandstrom H, Lingfors H, Erhardt L, Hedback B, Israelsson B, et al. Gender differences in secondary prevention of coronary heart disease: reasons to worry or not? Scand J Prim Health Care 2003;21(1):37-42.
169. Jonasson L. Markers of inflammation in women. In: Schenk-Gustafsson K, editor. The female heart - cardiovascular disease in women. Lund, Sweden: Studentlitteratur; 2003.
170. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342(12):836-43.
171. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. Circulation 1998;97(5):425-8.
172. Muhlestein JB, Horne BD, Carlquist JF, Madsen TE, Bair TL, Pearson RR, et al. Cytomegalovirus seropositivity and C-reactive protein have independent and combined predictive value for mortality in patients with angiographically demonstrated coronary artery disease. Circulation 2000;102(16):1917-23.
173. van den Bosch MA, Bloemenkamp DG, Mali WP, Kemmeren JM, Tanis BC, Algra A, et al. Hyperhomocysteinemia and risk for peripheral arterial occlusive disease in young women. J Vasc Surg 2003;38(4):772-8.