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Epidemiological Aspects of Peripheral Arterial Disease

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Abstract

Peripheral arterial disease (PAD) is defined as atherosclerosis in the arteries distal to the aortic bifurcation, with or without symptoms in the legs. It is diagnosed by ankle brachial pressure index (ABI) measurements and symptoms, and a confirmed diagnosis is associated with an increased cardiovascular (CV) mortality reaching the same levels as in patients with symptomatic coronary disease. The overall aim of this study was to describe PAD epidemiology and its consequences from a societal perspective with special focus on sex differences.

Eight-thousand subjects, aged 60-90 years, were selected at random and invited to participate in a survey performed in 2004. Of those 63% participated and had their ABI measured and they also completed questionnaires covering medical history, current medication, PAD symptoms and walking ability. A subset of subjects with intermitten claudication (IC) at inclusion was followed up 2008 with the same procedures. A walking test and duplex scanning of leg arteries, echocardiography and an interview were added to gain further insight of disease specifics. Survey data and published studies were finally used to estimate cost-effectiveness of CV risk prevention with drugs in subclinical PAD.

PAD prevalence was 18% and varied with stage of disease, geographic region and patients' sex. Women dominated when diagnosis was based on ABI only, but for diagnosis of IC, it was more frequent among men. The prevalence of critical limb ischemia was around one percent. Risk factor profiles differed among PAD stages and sexes. Men, for example, reported having diabetes mellitus, and stroke more often than women, who in turn reported hypertension more frequently. Smoking for 10 years was associated with having PAD in women, but for men this relationship occurred first after 30 years of smoking. Women also reported use of less CV preventive medication. Women with IC had a lower walking speed and more joint problems than men, and in the follow up cohort most IC disease specifics were similar. Another difference was that women reported atypical symptoms more often than men. The cost-effectiveness modelling revealed that of the evaluated drugs, ACE-inhibitors (ACE-i), statins, aspirin and clopidogrel, there were differences. ACE-i displayed the largest reduction of CV events leading to the highest mean gain in quality-adjusted life-years compared with the other treatments. It was far below the willingness to pay thresholds. Aspirin treatment did not appear to be cost-effective due to low rate of event reduction.

In conclusion, the studies performed in this thesis points out that PAD is common among elderly, and especially so in women. Risk factors occurring simultaneously with PAD are the known ones and many subjects with this disease have only PAD and do not report smoking habits. A majority is not medicating to reduce their high CV disease risk. Diagnosis of IC is a particular problem for epidemiological studies, and the prevalence of this PAD stage may therefore be underestimated in women. ACE-i may be the drug of choice for early prevention of CV risk in PAD and the benefits of aspirin may be overrated.

Keywords: Peripheral arterial disease, prevalence, risk factors, sex differences, diagnosis, intermittent claudication, preventive medication, cost effectiveness

List of Publications

I. Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Andersson B, Persson E, Wahlberg E
A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences
Journal of Vascular Surgery 2007; 45: 1185-91.

II. Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Wahlberg E
Risk factor profile and use of cardiovascular drug prevention in women and men with peripheral arterial disease
European Journal of Cardiovascular Prevention and Rehabilitation 2009; 16: 39-46

III. Sigvant B, Lundin F, Nilsson B, Bergqvist D, Wahlberg E
Intermittent claudication is the same disease in women and men but differs in presentation
Submitted

IV. Sigvant B, Henriksson M, Lundin F, Wahlberg E
Asymptomatic peripheral arterial disease: Is pharmacological prevention of cardiovascular risk cost-effective?
Submitted

Contents

List of Abbreviations

ABI	Ankle Brachial Index
ACE-i	Angiotensin-Converting Enzyme inhibitors
AP	Angina pectoris
APAD	Asymptomatic Peripheral Arterial Disease
ARB	Angiotensin-II Receptor Blocker
BMI	Body-Mass Index
BP	Blood Pressure
CAD	Coronary Artery Disease
CLI	Critical Limb Ischemia
CV	Cardiovascular
CVD	Cardio Vascular Disease (CAD,stroke and PAD)
DUS	Duplex Ultra Sound
DM	Diabetes Mellitus
EF	Ejection Fraction
HbA_{1c}	Hemoglobin A_{1c}
HC	Health care Centre
HDL	High Density Lipo protein
HMG-CoA	Hydroxymethyl glutaryl coenzyme A
HOPE	The Heart Outcome Prevention Evaluation study
HPS	Heart Protection Study
HR	Hazard Ratio
HRQL	Health related quality of life
HTN	Hypertension
IC	Intermittent Claudication
ICER	Incremental Cost Effectiveness Ratio
ICQ	Intermittent Claudication Questoinnaire
KPP	Swedish cost per patient register
LDL	Low Density Lipo-protein
MI	Myocardial Infarction
PAD	Peripheral Arterial Disease
PSV	Peak Systolic Velocity
PWV	Pulse Wave Velocity
QALY	Quality adjusted Life Years
QoL	Quality of Life
SBU	The Swedish Council on Technology Assessment in Health Care
SF 36	Medical Outcomes Study Short Form 36 Health Survey
SLI	Severe Limb Ischemia

SPPS	The Swedish PAD Prevalence Study
TASC	The Trans Atlantic Inter-Society Consensus Document
WHO	World Health Organization
WIQ	Walking Impairment Questionnaire
6MWT	Six Minutes walking Test

INTRODUCTION

Atherosclerosis is a process in the arterial tree affecting different vascular beds [1]. Peripheral arterial disease (PAD) is defined as atherosclerosis in the arteries distal to the aortic bifurcation with or without symptoms in the legs. It is important to view PAD from different perspectives; from an epidemiological perspective to achieve up to date information on PAD prevalence in different groups, from a societal where correct diagnosis and awareness are important for providing resources and preventive measures for cardiovascular disease (CVD), and finally from the patient's perspective, where symptomatic relief often is the number one concern. Decisions for diagnostic work ups and interventions, at least for intermittent claudication (IC), are mainly determined by patient's history, which makes interpretation of symptoms crucial for a correct diagnosis.

The PAD prevalence has been determined in many studies and is reported to be in the range of 15-20% in persons over 70 years old [2]. Few studies however are truly population based and data is lacking for some PAD stages as well as prevalence data for women. While the majority of elderly individuals in most western societies are women, most early studies enrolled only men. These results can not automatically be extrapolated to women, in a similar way as data for middle aged cohorts not are applicable for elderly. Furthermore, it is tempting to assume that risk factor occurrence that are well described for coronary arterial disease (CAD) and to some extent for IC, is the same for men and women and all stages of PAD. Finally, previously studies from countries in other parts of the world may not be applicable in local settings due to differences in risk factor exposition and socioeconomic conditions. New information of these poorly evaluated areas of PAD epidemiology is needed to provide a solid background for awareness programs and preventive efforts.

Awareness programs appear to be needed for PAD. One example of the former is that this patient group seems to be undertreated [3, 4], which is a severe problem because subjects with PAD face a three to seven times greater risk for early death due to CV events than a comparable population without PAD and this elevated risk is applicable also for asymptomatic (APAD) subjects [5, 6]. Another example in line with this concerns resource allocation for health programs. Increasing demands on vascular services are to be expected with an ageing population in most western countries and the need for epidemiological data on relevant population samples regarding prevalence, sex differences, risk factors and use of CVD preventive medication is important. In times of rising health care costs and limited resources implemented preventive measures must be cost-effective [7].
This thesis is trying to provide information of some of these epidemiological aspects of PAD.

GENERAL BACKGROUND

ATHEROSCLEROSIS

Atherosclerosis is the principal pathological process causing CVD. It is a degenerative disease characterized by the accumulation of cells, matrix fibres, lipids and tissue debris in the intima of the vessel wall, plaque formation. Eventually it may result in narrowing of the vessel lumen and obstruction of blood flow. One consequence is plaque ulceration that causes embolization or thrombosis. Another pathology contributing to both atherosclerosis formation and its consequence is that arteries will stiffen with age. This makes vessel less able to compensate for lumen obstruction caused by plaque formation and to respond to increased blood flow demand as during walking. The relationship between arterial stiffness and pulse wave velocity (PWV) was first predicted by Thomas Young in his Croonian Lecture in 1808 [8]. Increased aortic PWV predicts CVD, as well as CV mortality in individuals with hypertension (HTN), diabetes mellitus (DM) and in the general population [9, 10]. Accordingly, arterial stiffness estimations by PVW measurements may become a valuable clinical tool for prediction of CV risk and it is possible that APAD in reality is measure of this pathology [11].

Pathophysiology

Atherogenesis

The process of plaque formation has received a lot of scientific attention. While it used to be considered as a lipid metabolism disorder, it is today widely regarded more as an inflammatory disease [12]. In large parts the current view of the atherogenic process in PAD and other atherosclerotic diseases still focus on lipids. When plasma levels of cholesterol with low density lipo-proteins (LDL) rise, LDL particles are retained in the extra cellular matrix in the subendothelium of the arterial wall [13].There they initiate an inflammatory cascade and activation of endothelial cells that will express leukocyte adhesion molecules [14]. Circulating monocytes adhere to the wall and start to migrate into the underlying intima. Through cytokine stimulation, these monocytes are able to differentiate into macrophages expressing scavenger receptors. Proliferation of vascular smooth muscle cells from the media and secretion of extra cellular matrix compose the fibrous components, ongoing accumulation of lipid and inflammatory cell debris forms the necrotic lipid core of the mature atherosclerotic plaque [15].

Natural course

Depositions of these materials will subsequently thicken the vessel wall and eventually it compromises the vessel lumen. Until recently, atherosclerosis development was considered as a progressing process. Recently presented evidence pointed out that atherosclerotic plaque formation not necessarily is a constant process. There is now an abundance of data showing that plaque formation can be slowed, stopped or even reversed [16]. Arterial remodelling includes an age dependent dilatation at the site of progressive atherosclerosis that starts already in the 5th decade of life. This is an adaption in response to the atherosclerotic process [17]. Circulating cytokines and growth factors can in fact also facilitate vascular repair. One way is through attraction of bone marrow-derived mononuclear cells [18]. Intimal plaque volume may also decrease by resorption of lipids,

migration of cells out of the plaque and cell death. Another important mechanism is the formation of a fibrous cap that stabilizes the plaque and prevents rupture, embolization and bleeding [19]. The ability to reverse the atherosclerotic process may further be facilitated by drugs that reduce the inflammatory cascade e.g., the amount of lipids available for plaque formation, the risk for thrombosis and the ability for compensatory vessel enlargement with age.

Clinical Manifestations

Despite the fact that the entire arterial tree shares the same endothelium and genetic factors predisposing atherosclerosis, only a few areas are prone to develop atherosclerotic plaques and lesions. These areas are characterized by the fact that the blood stream causes irregular or low shear forces against the endothelium. Common locations for this are at bifurcations and vessel segments that are influenced by external factors such as bending sites and tissue that restricts outward remodelling. An explanatory hypothesis is that the activity of the endothelium is regulated by different rheologic conditions [20]. The arteries in the lower extremities are prone to develop atherosclerotic plaques, whereas vessels in the upper extremities usually are spared. This may be caused by differences in hydrostatic pressure influences and that lower extremities are much more subject to variations in flow rate caused by changing metabolic needs in the skeletal muscles according to the physical activity [19]. It is plaque composition rather than plaque size or stenosis severity that appears to be the main factor for a vascular event in the coronaries. Consequently, thrombosis formation is mainly caused by plaque disruption [21]. The same etiology is suggested for the carotid arteries but blood thrombogenicity also seems to matter at this location [16, 22]. Muscular peripheral arteries, such as in the legs, differ in other ways from the elastic central arteries. For example, they are able to respond to chronic changes in blood flow. Size and blood flow volume in peripheral arteries will adjust to the metabolic needs of the corresponding extremity musculature with adaption of vessel calibre [23]. Despite differences, atherosclerosis is systemic in nature, and CV conditions such as PAD, CAD and stroke often occur simultaneously (Figure 1).

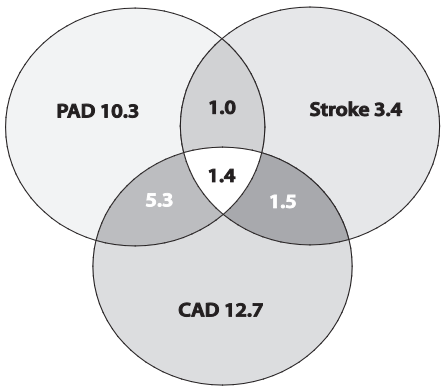

Figure 1 Prevalence of concurrent vascular diseases in the Swedish PAD Prevalence Study (Unpublished data).

In summary, while PAD is a manifestation of atherosclerotic disease among others it has unique features. PAD is often caused by rather benign plaques that seldom will rupture or bleed.

RISK FACTORS

The basic causes and risk factors associated with CVD in general are considered similar regardless of which vascular territory that is affected but in contrast to patients with CAD and stroke less is known about PAD patients' state of risk factor burden. Furthermore, most studies concerning PAD patients' risk factor profile has focused on IC and little is known about the other stages of PAD. CV risk factors for PAD subjects from a

population perspective are lacking to a large extent, and especially its implementation in subjects with different stages of PAD and possible differences between the sexes.

Age

As for stroke and CAD, the PAD prevalence increases with advancing age. The prevalence of any type of PAD among individuals aged 40-59 years, 60-69 years and >70 years is suggested to be 3%, 8% and 19%, respectively in the US [24]. Corresponding data for Europe among individuals (recruited at General Practitioner's offices) aged 70-74, 80-84 and >85 years is 16%, 26% and 33%, respectively [25].

Diabetes mellitus

DM increases the risk of CV morbidity and mortality. Numerous studies have shown an association between DM and an increased prevalence of PAD [26-28]. Individuals with DM have a 2 to 4 fold increased rate of PAD compared to subjects without diabetes [27]. It changes the nature of PAD due to the abnormal metabolic state that will alter functions of the endothelium, smooth muscle cells and platelets [26]. Hyperglycemia per se seems to be more strongly associated with PAD than CAD. For example a one percent increment in hemoglobin A_{1c} (HbA_{1c}) is associated with a 28% increased risk of developing PAD [29] emphasizing the need for optimal DM control. Subjects with DM have a tendency to develop PAD earlier in life compared to non-diabetic patients and they are more likely to be affected by the symptomatic forms of PAD [30]. PAD in DM patients is often more diffuse and distal distribution of atherosclerotic lesions is common. This explains the poor prognosis and the higher risk of lower extremity amputation, as well as the doubled mortality rate in general for PAD subjects with DM compared to those without DM [31, 32]. Subjects with PAD and DM also have poorer lower extremity function than those with PAD alone, which not only can be explained by the diabetes-associated neuropathy. Another contributing factor for the walking impairement among DM patients is neuropathic leg pain at exertion and rest, with and without association with IC. Subjects with DM are also shown to have a greater association with other CVD, such as angina pectoris (AP) and stroke. This can aggravate a limited walking capacity [33].

Smoking

According to World Health Organization (WHO) there are currently 1.1 billion tobacco smokers world wide, which is about a third of the world population aged 15 years and older. Smoking is a potent risk factor for PAD, displaying a consistent dose-response relationship [34]. The severity and progression of the disease, including the risk for amputation, are argued to be related to ongoing smoking habits [34-36]. In myocardial infarction (MI) and stroke the smoking effect seems to be reversible but it is not clear if this is the case for PAD. It seems to be a persisting high risk for developing PAD in former smokers which emphasises the need to prevent from ever starting to smoke [34]. It is furthermore suggested that cigarette smoking is a stronger risk factor for developing PAD than CAD. It is doubled compared to AP in smoking subjects, and the explanations for this may be differences in anatomical structures and hemodynamics [37]. Smoking habits are changing in Sweden as in other countries. A higher proportion of younger women are smokers today [38] and it is possible that young women may be more sensitive for the negative smoking effects [39]. It is plausible that changing smoking habits will alter PAD prevalence in the future.

Hypertension

Whereas HTN is strongly related to the risk for developing CAD and stroke, its association with PAD is contradictory. It has been evaluated in epidemiological studies focusing on IC. In the Framingham and Edinburgh studies a relationship between HTN and IC was observed, but not in the Reykjavik and Whitehall studies [40-43]. One explanation for these mixed results can be the fact that HTN apart from the associations with CVD in fact contributes to the pathogenesis of atherosclerosis [44]. The link may be the arterial stiffness pathology mentioned before and various studies report that increased pulse pressure is an independent risk factor for mortality in patients with HTN [10, 45, 46]. Fifty to eighty percent of patients with symptomatic PAD have HTN [25, 47, 48] and the combination of HTN and PAD increases the risk of having a CV event with 48% [49]. It is unknown if women with HTN have different association with PAD than men.

Hyperlipidemia

Elevated total cholesterol increases the risk for PAD [27, 41, 42, 50], and subjects who ultimately develop IC tend to have higher levels of cholesterol compared to asymptomatic subjects [41, 42, 51]. The Rotterdam study indicated differences between the sexes, with a significantly elevated total cholesterol only among women with PAD [52]. It has also been reported that PAD subjects have a broader lipid abnormality than patients with CAD and more often have low high density lipo-proteins (HDL) and hypertriglyceridemia [53].

Sex

On average, women develop heart disease 10–15 years later than men and also in PAD are women with symptomatic disease older [54]. The explanation is not clear and the hypothesis that endogenous estrogen is cardioprotective in women has received most attention. However, upon closer examination this evidence is not persuasive. Clinical trials have not shown that menopausal hormone replacement therapy is CVD protective, and recent trials have, on the contrary, shown prothrombotic effects. Accordingly, estrogen is no longer recommended for CVD prevention [55, 56]. Another proposed explanation is that the age difference is an adverse effect of androgens. Up until puberty young men and women have similar HDL-cholesterol levels but at puberty, concurrent with the rise of in testosterone levels the HDL cholesterol levels decline in men. Women have 20% higher HDL-cholesterol levels than men which predicts a lower risk of developing CVD. So the sex difference in CVD risk may be due to HDL-cholesterol levels as a consequence of the Y chromosome [57, 58].

Women with certain risk factors also appear to have a different risk for developing PAD than men. The Framingham cohort reports a 3.5-fold increased risk of IC in men with DM compared to the much higher 8.6-fold risk in similar group of women [59]. Smoking seems to affect the vessel wall differently in men and women. The intima and media thickness in carotid and femoral arteries is increased in male smokers but not in premenopausal women. Additionally is an increased stiffness in the aorta reported to be present in female smokers compared to non-smokers, a difference not found in men [60, 61]. Besides this there are little data in the literature on possible differences in risk factor profiles for men and women with PAD.

Race

The characteristics in risk factors for PAD in different ethnic groups for developing PAD are not fully understood. It is probable, however, that groups with a high prevalence of certain risk

factors associated with PAD risk also are at risk for PAD per se. One example is DM. A recent published review article from the UK determined the prevalence of type-2 DM to be much higher in African Caribbean's and South Asian groups compared to the general population [62]. Corresponding data from the US reports more DM and a higher body-mass index (BMI) amongst African-Americans compared to non-Hispanic Whites [63]. Data on risk factor profiles in PAD among ethnic minorities in Sweden is lacking.

In summary, while risk factors for PAD development and occurrence in patients with PAD are similar to other CVD according the literature to a large extent, there seems to be differences. PAD are more strongly associated with DM and smoking compared to other CVD and lipid abnormality profiles may differ.

PAD CLASSIFICATION

Different perspectives

Diseases associated with an impaired blood flow to the lower limbs due to atherosclerosis has been given many names e.g. lower limb ischemia, peripheral arterial disease, non-cardiac vascular disease and peripheral arterial occlusive disease. This basic problem with nomenclature may contribute to gaps in understanding of this disease. It is by large a matter of what perspective on PAD you have. For epidemiological questions the advantages of a uniform nomenclature and definition are obvious, because it makes it possible to identify appropriate cohorts. From a clinical perspective the consensus is to use definitions of disease that identifies only individuals who may undergo an intervention. Besides general patient risk the severity of symptoms is the main factor, to be indicative of treatment, so a consistency in classifications of different PAD stages is important from this perspective. This is also the perspective for clinical trial design. The patient's point of view is without considerations of classifications. It is rather high awareness, detection of the disease and information on treatment possibilities that matters. Health authorities are expected to protect health, guarantee access to health care and in times of increasing needs and demand, a correct disease classification is of importance for health care policies and for allocating funds.

Classifications

Several classifications of the different PAD stages have been proposed over the years. The Trans Atlantic Inter-Society Consensus document (TASC) have defined IC as muscle discomfort in lower limb reproducibly produced by exercise and relieved by rest within 10 minutes. Critical limb ischemia (CLI) is defined as chronic ischemic rest pain, ulcers or gangrene attributable to proven arterial occlusive disease. The systolic ankle pressure is usually <50 mmHg and toe pressure <30 mmHg, and if ulcers or gangrene is present the ankle pressure is <70 mmHg or toe pressure <50 mmHg [2]. Other classifications of PAD made by Fontaine and Rutherford and are presented in Table 1.

In summary, nomenclature and classifications of PAD are inconsistent. This may be explained by the great variation of disease presentations in symptoms and depend on the perspective of PAD that is at issue.

Table 1 Classification of peripheral arterial disease

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

EPIDEMIOLOGY

Vascular events, such as MI, stroke and PAD has for many years been the major causes of death and disability in the western world. Studies indicate that over the next two decades CVD will become the most common cause of mortality and morbidity worldwide [64]. Epidemiological data on non- coronary atherosclerosis are scarc and tends to be straggling [24]. The prevalence of PAD depends on the population studied, diagnostic methods used, and whether symptoms are included or not in the data sampling. Collection of current prevalence and incidence data for both clinical and subclinical vascular disease is important for comparison and understanding of similarities and differences in perspectives as ethnicity, sex and risk factors in order to face the increasing demands of CVD. Adequate comparison of data by different investigators is difficult since there is no consistency in either nomenclature or definitions. Additionally, there are few studies that strictly are population based, and few have included all stages of PAD. Another problem is that the data gathering is based on different criteria in the studies (Table 2).

Sex differences

In contrary to CAD, little attention has been paid sex differences in PAD prevalence. Older studies determining IC prevalence, for instance, included only men [51, 65, 66]. A majority of studies reports a higher prevalence of IC among men than in women. The question is, however, if this is a consequence of the IC definitions used in epidemiological studies or if it reflects a true difference in prevalence between the sexes. Prevalence data of different PAD stages among men and women are presented in Table 3.

Race

Understanding if there is a difference in PAD epidemiology in ethnic groups is relevant, not only from world health care perspective but also nationally and locally. Ethnic minority groups are steadily increasing in size in many western countries as an effect of migration, and these changing trends may effect PAD prevalence. Many epidemiological PAD studies have focused predominantly on Caucasian populations, but in a recent review the PAD prevalence in different ethnic groups varied remarkably. In South Africa (black African>50 years), China (Chinese >60 years), US (Hispanic >55 years), Saudi Arabia (Arabic >45), and Thailand (Thai aged 52-73) the PAD prevalence was 29.3%, 19.8%, 13.7%, 11.7%, and 5.2% respectively [62]. The high prevalence in Black Africans for instance, can only partly be explained by a heavy load of risk factors [63]. Genetically based differences in thrombotic and inflammatory factors may also contribute [71].

Table 2. Prevalence of PAD

Study	Country	Year	Sex	No	Age	Definition of ABI	Prevalence of PAD (Stage of PAD)
Böthig*	Russia	1975	Men	1326	50-54	Not measured	6.9% (IC)
[65]	Germany						3.4% (IC)
Reunanen*	Finland	1982	Men	5738	30-59	Not measured	2.1 (IC)
[66]			Women	5224			1.8 (IC)
Criqui	US	1985	Men	275	38-82	≤0.80"	11.7 "(Any PAD)
[67]			Women	338			11.7 "(Any PAD)
Fowkes*	UK	1991	Men	809	55-74	≤0.9	18.3 ¤"(Any PAD)
[50]			Women	783			18.3 ¤"(Any PAD)
Newman	US	1991	Men	82	≥60	<0.90	26.7¤(Any PAD)
[68]			Women	105			26.7¤(Any PAD)
Skau*	Sweden	1993	Men	2784¤	50-89	≤0.80	4.1 (SLI)
[69]			Women				
Stoffers*	Netherlands	1996	Men	1719	55-75	<0.95	16.5 (Any PAD)
[70]			Women	1935			17.0 (Any PAD)
Meijer*	Netherlands	1998	Men	3052	≥55	<0.90	16.9 (Any PAD)
[52]			Women	4663			20.5 (Any PAD)
Diehm	Germany	2002	Men	2890	≥65	<0.9	19.8 (Any PAD)
[25]			Women	3990			16.8 (Any PAD)
Selvin	US	2004	Men	2174¤	≥40	<0.9	4.5 (Any PAD)

* Population based
"Different non-invasive measurements were used to asses PAD prevalence
¤ No gender specific results were reported
IC Intermittent Claudication,
SLI Symptomatic Leg Ischemia

Table 3. PAD prevalence among men and women with different PAD stages.

	Men % (95% CI)				Women % (95% CI)			
STUDY	**Any PAD**	**APAD**	**IC**	**CLI/**	**Any PAD**	**APAD**	**IC**	**CLI/ SLI**
Criqui	11.7*	No data	2.2	No data	11.7*	No data	1.7	No data
[67]	(9.2-14.2)		(0.5-3.9)		(9.2-14.2)		(0.3-3.1)	
Fowkes*	18.3*	8.0*	4.5	No data	18.3*	8.0*	4.5	No data
[50]	(16.4-20.2)	(6.6-9.4)	(3.5-5.5)		(16.4-20.2)	(6.6-9.4)	(3.5-5.5)	
Newman	13.9	No data	2.0*	No data	11.4	No data	2.0*	No data
[68]	(12.5-15.3)		(1.6-2.4)		(10.2-12.6)		(1.6-2.4)	
Skau*	No data	No data	No data	4.5	No data	No data	No data	3.8
[69]								
Stoffers*	11.0	No data	1.5	No data	8.6	No data	2.8	No data
[70]	(9.5-12.5)		(0.9-2.1)		(7,4-9.8)			(2.1-3.5)
Meijer*	16.9	No data	2.2	No data	20.5	No data	1.2	No data
[52]	(15.4-18.3)		(1.7-2.8)	(19.2-21.8)			(0.9-1.5)	
Diehm	19.8	No data	3.6	No data	16.8	No data	2.3	No data
[25]								
Selvin	4.5	No data	No data	No data		No data	4.2	No data
[48]	(2.9-6.1)						(2.8-5.6)	

APAD Asymptomatic PAD
IC Intermittent Claudication
CLI/SLI Critical Limb Ischemia/ Symptomatic Limb Ischemia
*Prevalence in total population, no sex differences reported

Accordingly, as available data is incoherent the prevalence of IC and any stage of PAD varies greatly. For IC and any stage of PAD, for instance, it is reported to be between 1.8-6.9 % and 4.2-26.7 %, respectively (Table 2).

Geographic dissimilarities

It is possible that the PAD prevalence differs between regions in larger countries. While ethnic, environmental and genetic factors may be responsible for this there are uncertainties of the magnitude and causes of this problem. As an example, there are some indirect indications that PAD prevalence differs between Swedish regions. According to Swedvasc, the national register of performed vascular procedures in Sweden, the number of interventions for PAD varied from 80/100.000 inhabitants in the northern region to 132/100.000 in the South-East region [72]. This variation seems stable over time. Inequalities in health care resources may contribute to this phenomenon. The life expectancy can be used as an indicator of health and there are variations in different demographic and geographic regions in Sweden. The longest average life expectancy is found in regions with high socioeconomic status. For women the shortest life expectancy is found in industrial regions were CVD is highly prevalent. Alcohol related diseases and suicide were more related to premature death among men in big cities [73]. The specific reason for any such dissimilarity in PAD prevalence between different geographic regions in Sweden is not known.

In summary; prevalence data on PAD vary and this variation may partly be explained by inconsistency in nomenclature and definitions. A majority of studies report a higher prevalence for IC among men and data for CLI is lacking. Race and regional differences may also influence PAD prevalence.

COSTS AND QUALITY OF LIFE ASSOCIATED WITH PAD

One important aspect of PAD epidemiology it is to consider the costs for treating this disease and evaluation of the economic impact of PAD is important for assessing the cost-effectiveness of preventive, medical, endovascular, surgical and rehabilitative interventions. To day the economic impact of CVD is immense. In the US for example, it costed $ 403 billion (€270 billion) in 2006 compared with $ 190 billion (€ 127 billion) for cancer [74]. According to the Swedish Cost Per Patient (KPP) registry, costs for the first year after diagnosis of PAD, stroke and MI is 267.000 SEK (€ 26.000), 179.000 SEK (€ 17.000) and 241.000 SEK (€ 23.000), respectively [75]. Of these expenditures 75-88% is estimated for inpatient care [76, 77]. Symptomatic PAD is the most costly of all symptomatic CVD manifestations and it is also associated with the lowest quality adjusted life years (QALY). QALY is a measure of quantity and quality of life where one is full health and zero is death. The estimated QALYs for PAD (in this case IC) is 0.51 as compared to 0.73 and 0.69 for MI and stroke [78-80].

In summary, PAD is associated with the highest costs and lowest QALYs of the different CV manifestations.

DIAGNOSTICS

Diagnosis of PAD is essential for determining patient need, aiding clinical decision making and optimizing care. There are many examples of this. Firstly, subjects with any stage of PAD have a high risk of both fatal and nonfatal CVD events [5, 81]. Secondly, walking may be a painful experience for IC patients and CLI patients often depend on assitance for daily life activity because of their impairment of functional status. The reduction in health-related quality of life (HRQL)

of a person with IC is lower than for other serious illnesses, such as chronic lung disease or some forms of cancer [82]. Thirdly, when the life expectancy in western countries is rising clinical care of CVD will be prolonged with increasing costs as a consequence [64]. Accurate identification of PAD groups is important for decision makers to enable priorization between competing diseases and therapeutic options.

Medical history and examinations

In order to evaluate further treatment options it is important to map functional status as well as quality of life (QoL) to figure out the potential impact of the PAD on the patient's life. There are several diagnostic tools available that are suitable for different health care settings. The most frequently used are presentented in Table 4.

There are numerous diagnostic options and the ones used depend on the perspective it is needed for (see also page19). Diagnosis of APAD is simple made by measuring ankle and brachial systolic blood pressures. Ankle brachial index (ABI) is calculated by dividing the ankle blood pressure with the brachial one. APAD is present if the patient don't have leg symptoms and ABI<0.9. IC diagnosis is less straightforward. Diagnosing IC is difficult, also from an epidemiological perspective because it is based on subjective symptoms. The perceived disability and need varies between age groups, individuals and possibly between sexes and ethnic groups. In some circumstances ABI criteria is added to diagnostic criteria for IC.

Classical IC symptoms (which means to limp) are muscle discomfort in lower limb reproducibly produced by exercise and relieved by rest. The symptoms are most commonly localized to the calf, but may also affect thighs or buttocks. Patients may describe muscle fatigue, aching or cramping on exertion that is relieved by rest. This typical IC symptom occurs in up to one-third of all patients with PAD [83]. Potential differences in symptom presentation and diagnosis of IC need to be further investigated and highlighted since differences in prevalence may be due to inaccurate diagnostic methods.

Measurement of ABI is a standard part of the evaluation patients with suspected PAD and the cut off value is <0.9. Although ABI is a fairly sensitive indicator for PAD it is associated with several shortcomings. For example, calcified vessels that can be found in subjects with DM present difficulties. These vessels can become non-compliant, leading to an increased ABI (>1.4) or a normal ABI despite severely impaired blood flow to the leg [84]. Detection of IC, with proximally distributed lesions in the arterial tree may also influence ABI readings. A patient with IC symptoms due to a severe stenosis in the iliac artery may have normal ABI at rest. The vast majority of subjects with PAD can be detected by ABI measurement and therefore is suitable for epidemiological studies [85, 86].

CLI constitute ischemic pain at rest and may be associated with tissue loss. In most cases, the patients have foot pain that is intolerable and patients will seek medical attention. About one-fourth of the arterial foot ulcers are diabetic, and as mentioned above, the ABI may be within normal limits due to incompressible vessels [87].

In summary, diagnostic methods for PAD depend on whether it is needed for epidemiological research or for the clinical situation. While APAD is simple to define by means of ABI testing, IC diagnosis remains difficult and may be undetected and misinterpreted.

Table 4. Non-invasive and invasive vascular diagnostic tools for diagnosing PAD

Diagnostic Tool	Benefits/Limitations	Distribution/Severity/ When to use
Ankle-Brachial Index (ABI)	A non-invasive, quick, simple, cost effective method. Predictor of CV morbidity and mortality May not be accurate if pedal vessels are incompressible. Sensitivity and specificity 95% Variation coefficient<9.%	ABI do not determine distribution of lesions but severity of disease. For clinical and epidemiological purpose.
Toe-Brachial Index (TBI)	A non-invasive, cost-effective method to use when ABI is not reliable. Requires careful technique and small cuffs.	TBI do not determine distribution of lesions but severity of disease. For clinical and epidemiological purpose.
Questionnaires	A quick and standardized way to collect information. May describe ambulatory and HRQL limitations, and co existing problems limiting walking ability. Risk of misinterpretation, time consuming to analyse and process data.	Distribution of disease is not determined. For clinical and epidemiological purpose.
Walking test	May differentiate IC from pseudo IC Useful to diagnose IC when ABI is normal. Documents magnitude of symptom limitation.	Related to functional status and severity of IC. For diagnosis of IC, evaluation of treatment outcome, for clinical and for epidemiological use.
Duplex Ultra Sound (DUS)	Non-invasive, cost-effective Can establish PAD diagnosis, and distribution of lesions. Diminished accuracy in proximal aorto-iliac segment as for dense calcification. Sensitivity is diminished in distal lower limb segment. Reliability is investigator related.	Can localize distribution and disease. Useful to select candidates for revascularisation and for graft surveillance.
Contrast Angiography	Definitive method for anatomic evaluation of PAD Invasive method, with risk of bleeding, infection and access complication. Contrast allergy, nephropathy .	Can localize distribution and severity of PAD. Mapping preoperatively.
Computed tomographic angiography	Fast scan time. Can establish PAD diagnosis and distribution of lesions. Provides information of associated soft tissue (e.i aneurysm). Metallic material does not cause artefacts. Accuracy and effectiveness is less compared to MRA. Venous opacification may obscure arterial phase. Contrast allergy or Nephropathy, radiation exposure. Time consuming to analyse images. Sensitivity and specificity ≤80%	Can localize distribution and severity of PAD. Useful to select candidates for revascularization, visualise aneurysm. Safe to use for patients with pace maker.
Magnetic Resonance Angiography (MRA)	Non invasive, pain free method. Can establish PAD diagnosis and distribution of lesions. Tends to overestimate degree of stenosis. Can not be used in patients with pace-maker, stents, clips or other metallic devices. Sensitivity and specificity ≤80%.	Can localize distribution and severity of PAD. Useful to select candidates for revascularization.

TREATMENT

Treatment of PAD consists of two main strategies. The first one aims to prevent CV events and the second strives to relieve symptoms. Because atherosclerosis develops insidiously over many years and usually is advanced when PAD symptoms occur, death from CVD may happen suddenly and before preventive measures are instigated. This is a pity since modifications have shown to reduce CVD morbidity and mortality [88, 89]. CVD preventive measures can in addition to individual benefits also reduce societal costs [90]. Primary drug prevention treatment for subclinical PAD should, according to the Swedish Medical product agency [91] only be considered after evaluation of individual risk despite the fact that a lowered ABI, regardless of symptoms is highly associated with an increased risk for CVD events [5, 92]. The lack of cost effectiveness data may contribute to this recommendation. Below follows more details about current treatment recommendations.

Life style

Smoking

As described previously is smoking a proven strong risk factor for development and deterioration of PAD. Smoking cessation advice is therefore fundamental for PAD patients. Quitting smoking is very difficult for the patient with addiction seriousness at the same level as opiate dependency [93]. Spontaneous cessations rates without intervention range from 2% to 5%, despite the fact that nearly 75% of smokers express a desire to stop. In one study only 5 % of patients who received physicians' advice stopped smoking versus almost none if the physician did not mention the smoking habit at all [94]. Behavioural interventions can improve these figures, but not much [93, 95]. Pharmacologic therapies are more effective than medical advice alone. Nicotine replacement strategies accomplish smoking termination rates between 11% and 34% at one year [96]. Nicotine replacement is also cost-effective [97]. There are other drugs that may improve cessation rates even further. One example is Bupropion, which is an "atypical" anti-depressive drug, with fairly high rates of smoking cessation compared to placebo (OR 2.04 95% CI 1.73-2.55). A newer drug, Vareniklin, is a nicotine receptor-agonist, that has shown better results (OR 2.41 1.92-3.12) with a good tolerability and in this context, a low relapse rate [98].

Exercise therapy

Physical activity is a crucial factor for the success of both primary and secondary CVD prevention in PAD patients. Studies indicate an inverse dose-response relationship between overall physical activity and the risk for CVD, which is linear at least up to a certain level of activity [99]. Exercise therapy also significantly improves walking ability in patients with IC. Most of these data come from trials employing supervised exercise programs consisting of 30-60 minutes exercises three times a week. This recommendation is also what is included in most guidelines. In a Cochrane meta-analysis the maximal walking time improvement was 6.5 minutes. This corresponds to a 1-3 fold increase over the baseline data [100]. Even more impressive are the results from Nordic Pole walking studies. In one of them the walking time in IC patients increased with 18 minutes [101]. Besides walking times exercise training also improves HRQL [102]. Unsupervised exercise training program has substantial long-term benefits to a modest cost. More expensive supervised exercise program are also cost-effective for most individuals with CVD [103].

The mechanisms behind its improvement capacity are proposed to include optimized endothelial function and metabolic adaptation of the skeletal muscle. Development of collateral vessels with

an improvement in blood flow may also contribute as well as more effective walking patterns [104, 105].

Pharmacological treatment

PAD patients need effective medical care for an extended period of their lifetime. Therefore, different treatment modalities have to be carefully evaluated. Recommendations by different guidelines, separated by PAD stage, are summarized in Table 5.

Anti-platelet therapy

The positive effect of anti-platelet therapy is likely to act through several different mechanisms. Aspirin inhibits thrombosis formation by decreasing the production of prostaglandins and thromboxans. Aspirin suppresses production of these factors by irreversible inactivation of the cyclooxygenase enzyme [106]. Clopidogrel, a thienopyridine derivate, acts through different mechanisms. It blocks activation of platelets by adenosine diphosphate which selectively and irreversibly inhibits binding to its receptor on platelets and thereby inhibit platelet aggregation [107].

Table 5. Recommendation of preventive medication according to current guidelines

	TASC		*ACC/AHA**		*European guidelines*	
	APAD	Symptomatic PAD	APAD	Symptomatic PAD	APAD	Symptomatic PAD
Anti-platelet						
Asprin	Can be considered if other CV manifestation	Recommended	Recommended	Recommended	Can be considered if high CVD risk	Recommended
Clopidogrel	Not recommended	"Is effective"	Recommended (alternatively to aspirin)	Recommended (alternatively to aspirin)	Not specified	Recommended (alternatively to aspirin)
Lipid lowering	To achieve LDL target levels (Initial dietary)	To achieve LDL target levels (Initial dietary)	To achieve LDL target levels (Statins)	To achieve LDL target levels (Statins)	According to current national treatment guidelines	To achieve LDL target levels (Statins)
Cardio protection	Not recommended	Not recommended	"Can be considered" (ACE-i)	"Is effective" (ACE-i)	"May be considered" (ACE-i)	"Is reasonable" (ACE-i)
Anti-HTN	To achieve BP target levels (Initial Thiazid and ACE-i)	To achieve BP target levels (Initial Thiazid and ACE-i)	To achieve BP target levels	To achieve BP target levels	According to current national treatment guidelines	To achieve BP target levels "(B-blockers are effective)"

* ACC/AHA American Association for Vascular Surgery, Societyter Vascular Surgery

Anti-platelet therapy is recommended to prevent associated CV morbidity and mortality in PAD (Table 5). Use of aspirin is based on analogous data in CAD and stroke patients, where anti-platelet therapy has a documented efficacy [108]. However it is recently shown to have different effects in men and women. Aspirin therapy reduced the risk of stroke but did not affect the occurrence of MI in women [109]. The Anti-thrombotic Trialists Collaboration summarized the results from 287 studies involving 135.000 patients rand-

omized to receive anti-platelet therapy or placebo. There was no reduction in CV events in PAD patients treated with aspirin who did not have other evidence of additional vascular disease. The recent reanalysis of this data found a significant clinical benefit also in the PAD group that consisted of 23% risk reduction in all subgroups of patients with PAD. In both these investigations anti-platelet therapy included aspirin as well as clopidogrel, ticlopidine, dipyridamole and picotamide [110].

The CAPRIE study compared clopidogrel with aspirin in patients with a high risk of CV events, including PAD subjects. More than 19 000 subjects were included. A small but yet significant reduction in the primary end-point of MI, stroke and vascular death was observed for clopidogrel. In a subgroup analysis of 6452 patients with PAD clopidogrel use resulted in a relative risk reduction of 24% compared with aspirin [111].

Lipid lowering therapy

The positive effects of statins are numerous and the action is not only mediated by its cholesterol lowering ability [112]. The main mechanism is inhibition of hydroxymethyl glutaryl coenzyme A reductase (HMG-CoA) that is the rate limiting enzyme for cholesterol formation in the liver and other tissues. By inhibiting HMG-CoA reductase, statins reduce the hepatocyte cholesterol content, stimulate expression of LDL receptors and ultimately enhance removal of LDL from the circulation. Statins seem to stabilize plaques so beneficial effects are reported independently of change in LDL levels [113]. Triglyceride concentrations are reported to be reduced by 22%-44% in patients with hypertriglyceridemia due to a decreased hepatic secretion of very-low-density lipo proteins. Statins further cause an increase in HDL with 5%-10% [114].

The Heart Protection Study (HPS) provides evidence for use of statins in patients with PAD. Simvastatin use was associated with a reduction of any vascular mortality, CAD events, stroke and non-coronary revascularizations by 17%, 24%, 27% and 16%, respectively. No specific target of plasma cholesterol concentration treatment goal was associated with the benefits, which occurred also in patients with low levels at baseline. More recent data also suggests that PAD symptoms may be improved by statin treatment. Pain-free and total walking distance was also increased by statins in a study evaluating it against placebo [115, 116].

Guidelines suggest that all PAD patients (including APAD) should have a LDL-cholesterol <2.59 mmol/L, and for subjects with other CV manifestations the level should be <1.81 mmol/L.

Anti-hypertensive treatment

Anti-HTN treatment prevents stroke and CAD. There are five major classes of anti-HTN agents-thiazide diuretics, β-blockers, calcium antagonists, angiotensin converting enzyme inhibitors (ACE-i) and angiotensin-II receptor inhibitors (ARB). They have different mechanism of actions. Thiazide diuretics decrease resistance in smooth muscle cells, β-blockers inhibit renin formation and decrease cardiac out-put. Treatment with calcium antagonists, ARB and ACE-i will lead to dilatation of resistance vessels by separate mechanisms [117]. Recent evidence suggests that the use of ACE-i in patients with PAD may offer protection against major CV events beyond those expected from only blood pressure lowering. These additional benefits may involve mechanisms such as reduction of oxidant stress, vascular and cardiac muscle hypertrophy [118] and it is also possible that ACE-i's effects on vessel wall compliance have benefits that not only are related to blood pressure lowering [119]. It is probable

that these effects are similar or even particularly strong in PAD patients.

The Heart Outcome Prevention Evaluation study (HOPE) demonstrated that the primary endpoint of CV death or nonfatal MI or non-fatal stroke among APAD was reduced by ACE-i treatment with 14%-19%, depending on level of ABI (clinical PAD 23%). It was about two-fold for subjects with low ABI values versus normal ABI [120].

In the past, β-blockers were avoided in patients with symptomatic PAD because of fears of vasoconstriction and deterioration of the peripheral arterial circulation. But a meta-analysis suggested that β-blockers do not adversely affect walking capacity [121]. One anti-HTN-drug, an α-blocker caused improvement of PAD symptoms examplified by an increased walking distance [122].

Guidelines suggest that anti-HTN therapy should be administered to hypertensive PAD patients to achieve a goal of less than 140 mmHg systolic over 90 mm Hg diastolic or less than 130 mmHg systolic over 80 mmHg diastolic for diabetics and/or individuals with chronic renal disease.

Diabetes mellitus

The Diabetic Control and Complication Trial and the UK Prospective Diabetes Study provided evidence of the benefits of glycemic control in microvascular disease (diabetic proliferative retinopathy and nephropathy) in patients with DM [123, 124]. The effect of glycemic control on macrovascular disease such as PAD is less definitive. Intensive insulin therapy does not significantly reduce large artery atherosclerotic events compared to usual diabetes care. Given that blood pressure and lipid levels are optimized evidence that a normalized HbA1c result in CV gains have become weaker in the literature [124].

Guidelines recommend an aggressive control of blood glucose levels with an HbA1c goal of <7.0%.

Invasive treatment

Determination of the optimal method for revascularization or treatment of PAD symptoms is based upon balancing the risk of a specific intervention and durability of improvement that can be expected from the intervention. This sometimes is a dilemma for the surgeon or interventionalist.

There is little scientific evidence available for supporting revascularization as treatment for IC symptoms, despite the fact that open surgical procedures are an established strategy since decades ago. The Swedish Council on Technology Assessment in Health Care (SBU) recently performed a systematic literature review on this subject and found only two out of 1687 articles evaluating open revascularization in IC in a systematic and randomized way [125]. Invasive treatment increased walking capacity on the expense of some more complications in these studies [126, 127]. SBU concludes that there is some evidence for open revascularization for IC symptoms. There is also evidence that QoL is improved by surgical treatment but this observation does not come from controlled studies. Patients perceived physical function is reported related to their risk attitude. Subjects with severe IC are willing to accept a substantial risk when it comes to surgical treatment, which is explained by the impaired health related QoL before treatment [79]. According to SBU evidence for endovascular treatment of IC symptoms is inferior to open surgery but despite the lack of data it is often the first treatment choice in many vascular centres [125]. The TASC document recommends that when choosing between techniques with equivalent short- and long-term clinical outcomes, the endovascular technique should be used first [2].

As for IC, there is little scientific evidence for treating CLI patients with revascularization to relieve symptoms; nevertheless it is widely used across the world. Open revascularization has some indirect support of being effective. The rate of amputations was 15-20% after one year, compared to 40-50% in a placebo group in a study with CLI subjects not feasible for any kind of revascularization [125]. CLI is afflicted with pronounced symptoms as rest pain and/or leg ulcers or gangrene with consequently low HRQL. For this patient group any kind of reasonable revascularization is favored to avoid limb loss and relieve pain [2].

In summary, treatment in PAD focuses on prevention of CV risk and relief of symptoms. For the former life-style modifications and smoking cessation are the cornerstones, along with drug treatment in some circumstances. Symptomatic relief can be achieved by revascularization but its effect has limited scientific evidence behind it.

AIMS

OVERALL AIM

To describe PAD epidemiology and its consequences from a societal perspective with special focus on sex differences.

SPECIFIC AIMS

1. To determine prevalence of all PAD stages among men and women in Sweden.
2. To determine CV co-morbidities associated with different stages of PAD and current use of pharmacological CV risk reducing therapy among men and women in with the disease.
3. To elucidate if IC is a different disease entity in men and women, with special focus on how the symptoms are perceived.
4. To evaluate the cost-effectiveness of treating subclinical PAD with CV event preventive drugs.

METHODS

An overview the population studied and methods used are given in Figure 2.

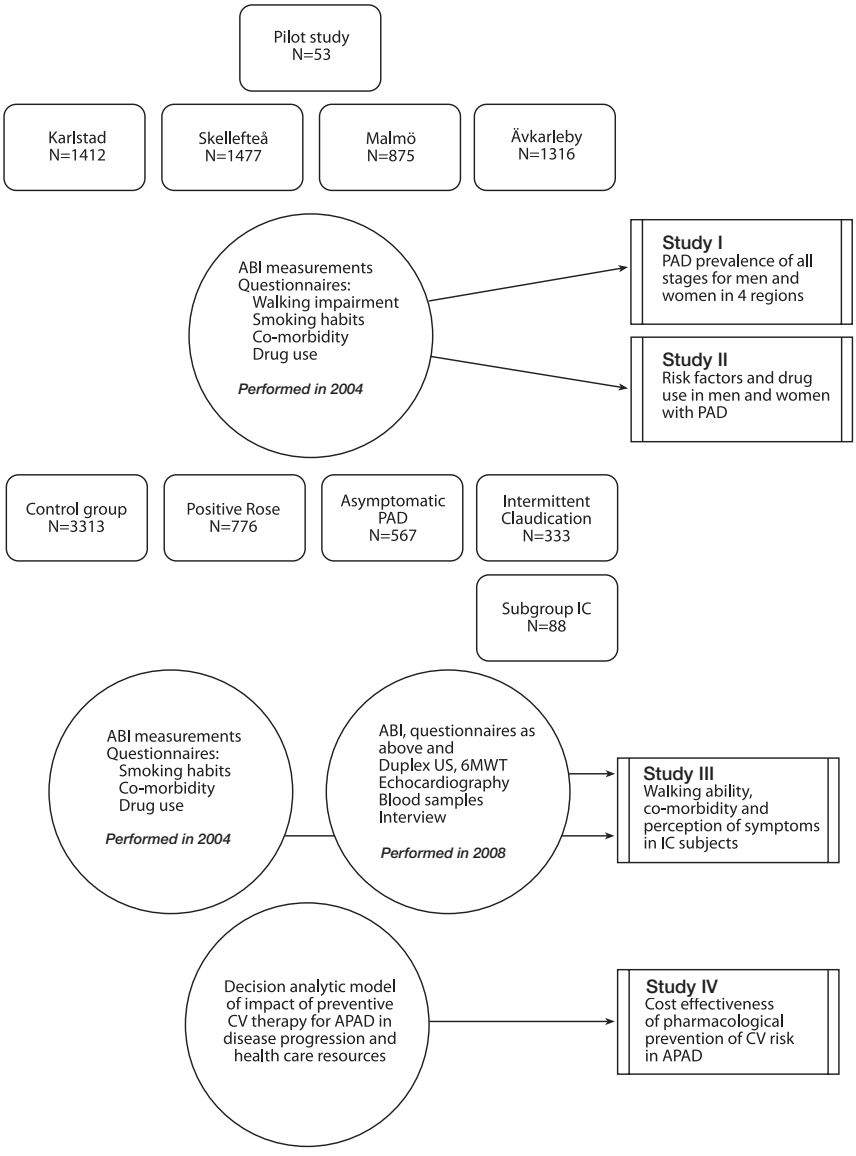

Figure 2. Population and methods used in the thesis.

STUDY DESIGN

The Swedish PAD Prevalence Study (SPPS)

Pilot study

A pilot study was performed in February 2004 to determine logistic factors influencing the final protocol and to estimate the sample size needed for the main study. The goal set was to identify at least 400 subjects with symptomatic PAD for later follow-up studies. The pilot study included 53 subjects aged 60-90 years, who were selected at random from a population register. The prevalence of overall PAD was slightly higher (32%) than expected so the sample size was therefore reduced from the estimated 10.000 subjects to 8.000.

SPPS main study (Study I and II)

SPPS is a population based point prevalence study covering men and women aged 60-90 years. Eight-thousand subjects from four separate regions in Sweden were enrolled (Figure 3):

- Karlstad: A mid-sized city with dominance of white collar workers
- Skellefteå: A rural area largely populated by farmers
- Malmö: A big city with a large population of immigrants
- Älvkarleby: A rural area with a small town and a large population of factory workers.

Figure 3. The Study population

Comment

Population samples from four different regions were selected to cover geographic and demographic differences in Sweden, and thus to make study results generalizable for the entire population. In 2004 ten percent of the population in Sweden was born outside the country or had parents who were immigrants [128]. Rosengård Health Care Centre (HC) in Malmö, that covers a population with 59% immigrants was selected to achieve a cohort with the same ethnical diversity as in Sweden.

Follow-up study (Study III)

This study combined data from SPPS and from a follow-up analysis of IC subjects in one of the regions. The follow up analysis was designed as a descriptive case–control study comparing men and women within the cohort. The results in Study I of an overall higher PAD prevalence among women, but a male dominance for IC raised the question if there is a “true” sex difference in IC prevalence or if it could be explained by other factors. The follow up study included all IC subjects at one site (Karlstad) (Figure 4).

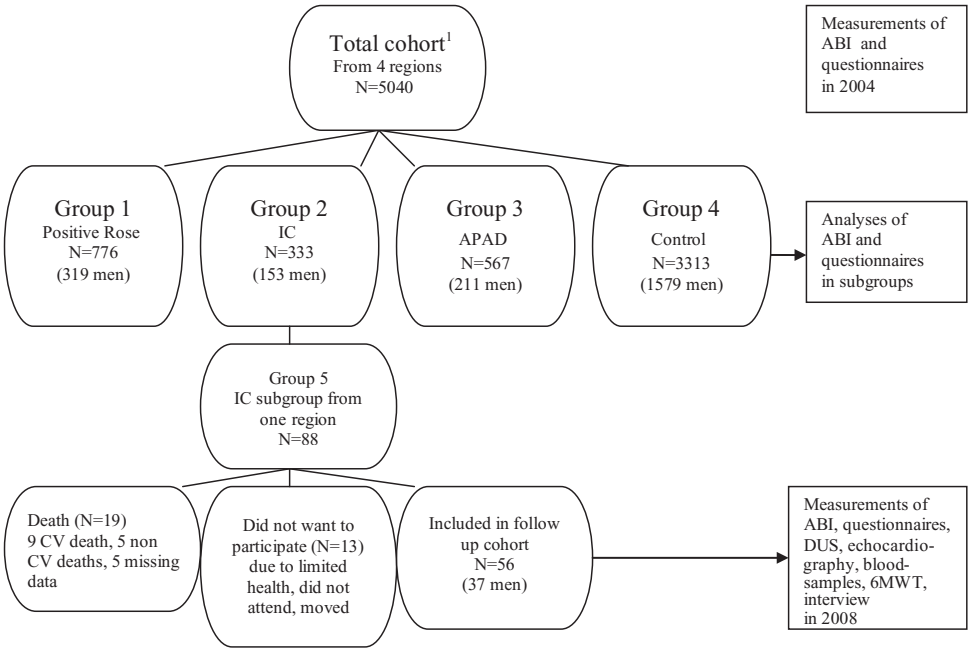

Figure 4. Flow chart of population and measurements performed in SPPS and the follow-up study (Study III)

1. Subjects with severe limb ischemia was not analysed in this paper

Group 1. Positive Rose Questionnaire, regardless of ABI
Group 2. ABI<0.9 and positive Rose Questionnaire
Group 3. ABI<0.9 and negative Rose Questionnaire
Group 4. ABI>0.9 and negative Rose Questionnaire

Group 5. Follow up in Karlstad ABI<0.9 and positive Rose Questionnaire

Comment

The region in the follow-up study had the highest PAD prevalence of all included regions but the distribution of PAD stages was consistence with the cohort as a whole. The Karlstad population had a slightly higher median age (72 versus 71 years) and consisted of more women (63% versus 55%) than in the total cohort. The sample size was quite small, but we nevertheless believed that it would be sufficient to determine large differences between sexes in the nature of IC disease. The final decision to only include one centre in the follow-up study was also influenced by available resources and practical considerations.

Cost effectiveness analysis (Study IV)

This part of the project employed data from SPPS, available literature and Swedish Health Care Authority data as sources for a mathematical modelling analysis. The purpose was a cost-effectiveness analysis, a form of an economic evaluation where both costs and consequences are considered [129].

The results are usually summarized as an incremental cost-effectiveness ratio (ICER);

$$ICER=(Ct-Cc)/(Et-Ec)=\Delta C/\Delta E'$$

Ct (Et) and Cc (Ec) are estimated mean costs (health outcomes) of the investigated treatment and the comparator. Costs refer to the resources used, both in the health care system (e.g. clinical staff, capital equipment, buildings and consumables such as pharmaceuticals) and outside the health care system (e.g. loss of production due to sick leaves). Effectiveness is measures by an appropriate health outcome. A commonly used health outcome is quality adjusted (QALYs) that combines mortality (quantity of life) and morbidity (quality of life) in a single measure.

Comment

A decision-analytic model will contain some simplifications, assumptions and uncertainties of parameter values. Taking these issues together, it is clear that the results of any decision-analytic model are associated with uncertainty. These uncertainties can not be resolved, but handled by different methods. The methodological principles of this model are performed in concordance with guidelines of a "reference case" [129, 130].

POPULATION

Men and women in Sweden, aged 60-90 years were the target population of the original SPPS cohort (Study I-III). Subjects living in the Karlstad region identified in the original survey in 2004 having IC were selected for follow-up in 2008 (Study III). Hypothetical subjects with APAD aged over 65 years were target population for cost analysis (Study IV).

Comments

The population of Sweden was 9.2 million in 2004 of whom 17% were over 65 years old [128]. In order to identify enough subjects with PAD for later follow up, especially with the more advanced stages IC and CLI, a cohort of elderly (60-90 years old) was selected. Cohort sizes were based on data from a pilot study. The age span was selected based on the assumption that PAD prevalence increases with age (Table 2).

METHODOLOGY

All subjects in SPPS (Study I-III) underwent ABI measurements. It is the most established test for diagnosis of PAD [131]. Standardization of ABI measurements was achieved by supervised monitoring. For further evaluation of walking capacity, was the Walking Impairment Questionnaire (WIQ) used [132]. This questionnaire quantifies walking capacity as well as other differential symptoms that may interfere with walking ability. A separate specially designed questionnaire recorded concomitant diseases, risk factors and medication use.

Four nurses at the four sites were employed carrying out the initial study. They attended courses covering PAD facts and were trained in ABI measurements. All had to pass a practical and theoretical test before study start. To overcome language barriers between nurses and subjects who did not speak Swedish in Malmö, staff was recruited who besides Swedish spoke other languages such as Turkish, Serbo-Croatian, Arabic and Kurdish. A coordinating nurse visited all sites several times during assessment time to monitor and validate the examination procedure and data recording process

Additional methods were used in the follow up IC cohort (Study III) (Figure 4). Intermittent Claudication Questionnaire (ICQ) added for further characterization of HRQL [133, 134]. This questionnaire combines walking ability assessment with correlates of the EuroQoL and Short Form

(SF-36). The two latter are generic instruments assessing HRQL. To further assess walking ability the six minutes walking test (6MWT) was added to the methodology because self-assessment of physical activity is subject to bias [135]. This data were then compared with the information gathered during a structured interview, which was a prerequisite for having detailed information on subjects' perception of symptoms. Duplex Ultra Sound (DUS) was used to map the distribution and amount of atherosclerotic lesions and echocardiography to describe any mobility restricting heart disease.

One vascular nurse executed all ABI measurements, 6MWT and interviews in Study III. DUS was performed by a vascular technician and the echocardiographies by three physicians. A methodological overview of the studies is given in Table 6.

Table 6. Methodological overview of Study I-IV

	Study I, II	Study III	Study IV
Design	Survey	Case-control	Decision-analytic model
Study base	Malmö, Älvkarleby Karlstad, Skellefteå	Karlstad	
Time period	2004	2008	2009
Patient group	Un selected population	Intermittent claudication	Asymptomatic PAD
Number of subjects	5080	88	
Men/Women (%)	55/45	42/58	
Age (median)	60-90 (71)	60-90 (77)	>65 years
Measurements	ABI, questionnaires	ABI, questionnaires DUS, 6MWT echocardiography and blood samples	Event rates. Risk reduction by treatment Utility. Costs
Data sources			Epidemiological studies Clinical trials Hospital registers Pharmaceutical lists

Comment

Concomitant diseases, drug use and smoking history were self reported in the project, which could lead to an underestimation of its occurrence. In the literature, however, self-reported data on smoking as an example produces an acceptable sensitivity and specificity of the true situation [136]. We believe that performed measurements were valid because of the education, training and repeated monitoring process used.

Cost study (Study IV)

The analytic framework for analyzing a decision model required the following main tasks [137]:

1. Constructing a decision-analytic model appropriately representing the clinical decision problem under consideration.
2. A probabilistic analysis of this model in order to determine cost-effectiveness and characterise current decision uncertainty.
3. Estimating the value of additional information of research to reduce decision uncertainty.

The presented study focused on the first two tasks that are necessary to determine cost-effectiveness given available information, leaving the third one for future analyses.

In the model CV events rates for APAD subjects

were retrieved from epidemiological studies and estimations of risk reduction by treatment of target drugs (those recommended in guidelines) from randomized clinical trials (Table 7).

Table 7. Available randomized clinical trials for hazard ratio estimates of risk reduction by different treatment strategies

Trial	Drug	Subjects (N)	Primary endpoint	Secondary endpoint	Follow-up time
HOPE	ACE-i	APAD (3099)	CV death, MI, stroke	All cause death, hospitalization for heart failure and diabetic complications	4.5 years
HPS	Simvastatin	CAD, arterial other occlusive disease or DM (20 536)	All cause mortality, fatal MI	Non coronary death, vascular events	5 years
POPADAD	Aspirin	DM and APAD ABI<0.99 (1276)	Composite endpoint[1] CV death	All cause mortality, MI or other vascular event	4.5-8.6 years
CLIPS	Aspirin	PAD stage I-II, APAD: 28% ABI<0.85 76% had DM (366)	Combined incidence of fatal and non-fatal vascular events		2 years
CAPRIE	Clopidogrel	Symptomatic PAD (5795)	Stroke, MI, vascular death	Amputation, vascular death	1.9 years

1. CV death, MI, stroke or above ankle amputation for CLI

Costs associated with the health states were the ones available in a large Swedish hospital based register (KPP) that collects costs of administration, hospitalization, diagnostic work-up, intervention and rehabilitation for each diagnosis. The 2009 price list from "Pharmaceutical Specialities in Sweden" (FASS) [138] was the basis for the pharmacological costs. Health outcome were calculated as QALYs for a particular health state and were derived from published sources.

Table 8 summarizes selection criteria for included studies where event rates were retrieved.

Table 8. Selection criteria in the literature review for event rates

- Population based
- Original clinical research report
- Written in English language
- Sex specific data should be available (missing for 2 of the drugs)
- The age distribution of the patients should be described
- The follow-up time should be given

Older epidemiological cohort studies

Comment

A number of assumptions were necessary because absence of probability data in some circumstances. We also needed to simplify the model. The main assumptions made were

• By choosing older epidemiological studies we assumed a negligible rate of treatment with the drugs evaluated. These data were used for "clinical practice".

• We assumed that background variables such as age, smoking, DM, CAD or stroke would not influence event rates differently in drug treatment and the clinical practice arm. In order to keep the model reasonably simple we therefore did not adjust the model according for these parameters.

• In the estimation of HR for event reduction in different treatment strategies. APAD data was used when available. Unfortunately, for statin and non-aspirin anti-platelet therapy data for APAD subjects was missing. We therefore used data for symptomatic PAD stages, supported by the literature claiming that HR for event rates following drug treatment are similar and not influenced by PAD stage [139].

•Since the model is based on assumingly retired persons we did not include indirect costs, assuming that this not would influence outcome. Uncertainty in economic evaluations can arise because of these methodological assumptions and data requirements. The need to extrapolate results over time and the desire to generalize the results to clinical practise may also create uncertainty. There are several methods for handling this, some of which were used in the Study IV.

DIAGNOSTIC CRITERIA AND DEFINITIONS

Definitions used in all studies were:

ABI	the ratio of the lowest systolic BP in the ankle divided by systolic BP in the arm [140]
Any PAD	as all subjects with an ABI<0.9 or >1.4 with or without symptoms
APAD	subjects with ABI<0.9 without qualifying answers in questionnaires (i.e.no pain in the calf or tights when walking)
IC	subjects with ABI<0.9 and qualifying answers in questionnaires (leg pain when walking with relief at rest)
SLI-1	subjects with ABI<0.9 and qualifying answers in questionnaires (leg pain when walking with relief at rest)
SLI-2	all subjects with ankle BP < 70mmHg and qualifying answers in questionnaires (i.e. pain in leg at rest)
CAD	congestive heart failure, stroke, DM and HTN were considered present if reported in the questionnaire and only those listed were used in the analysis
Smoking history and medication use	were up to participants' discretion
BMI	was calculated according to WHO standard (by weight and length from questionnaire data) and classified as under weight if BMI <18.5 kg/m^2, normal if BMI=18.5-24.9 kgm^2, overweight if BMI=25.0-29.9 kg/m^2 and obesity if BMI >30.0 kg/m^2 [141]
DUS	were stratified into four categories: 1.Normal (peak systolic velocity ratio (PSV) <2.5m/s, 2. Significant stenosis (PSV >2.5), 3. Diffuse disease (numerous lesions without any PSV alteration or PSV<2.5 and 4. Occlusion (absence of flow)[142]
EF	left ventricular ejection fraction by Simpson <50% was considered as an index if impaired systolic function [143]
QALY	as a measure of disease burden including both the quality and the quantity of life. The QALY is based on the number of years of life that would be added by the intervention. Each year in perfect health is assigned the value of 1.0 down to a value of 0.0 for death [145] .

Comment

One important question concerns which cut-off value of ABI to use for diagnosis of PAD in this project. The current guidelines published by the American Heart Association define ABI as the quotient of the higher of the systolic BP of the two ankle arteries of that limb (either the anterior tibial artery or the posterior tibial artery) and the higher of the two brachial systolic blood pressures of the upper limbs [146]. In this project we used the lowest ankle blood pressure (Table 1). The rational for this was to make sure that subjects with generalized atherosclerosis were included in the definition of APAD [140]. This reflects a more epidemiological perspective than a clinical one, and is important to consider when evaluating the prevalence data.

Another question important for Paper I and II is the definition of CLI. Diagnosing CLI in the epidemiological setting is known to be notoriously difficult and most definitions use a clinical perspective. The TASC group, for instance, recommends that manifest rest pain should be added to objective assessment of ankle blood pressure [2]. Unfortunately, reported symptoms are often difficult to interpret because differences in pain perception and etiology of ulcers can be difficult to define [87]. We therefore introduced the term severe leg ischemia (SLI) for this project. An ABI>1.4 was considered pathological, as a sign of an incompressible vessels for advanced PAD [139]

STATISTICS AND ETHICS

STUDY I-III

Statistical evaluation of the data was carried out with a computer software package (SPSS PC Version 12.0-15.0). Fishers exact test and X^2 test were used for comparison of normally distributed data and Mann-Whitney U test was used for comparison of non-normally distributed data. The test of equal proportions was used for comparisons of sex differences, prevalence of CV disease, medication use and smoking habits, accounting for the two stage cluster sample. Multiple logistic regression models were used for analyses of association between risk factors and PAD stages, interactions test, tests for confounding and influence of medication use on PAD prevalence. To adjust for confounding, multivariate logistic regressions were used. For correlations, Spearman rank correlations were tested for deviations from the null hypothesis using the usual asymptotic test.
P- values below level 0.05 were considered to be statistically significant in study I-III.

STUDY IV

All input to the Markov model such as event rates and treatment effects are crude rates extracted from randomized clinical trials. We used the person-year method to compute incidence rates for each event type. For event rates or treatment effects where multiple sources are available the estimates are averaged using the inverse of the variance (extracted from 95% confidence intervals) as weight.

ETHICS

All participants in SPPS gave their informed consent and were approved by the ethic committee in Stockholm (Dnr KI 03-538), Lund University (Dnr 832-0) and Uppsala University (Dnr 03-564, Dnr 2008/056) Örebro (Dnr 374-03), and a separate approval was obtained for Study III Uppsala (Dnr 2008/056).

RESULTS

PREVALENCE OF PAD IN SWEDEN

The PAD prevalence in Sweden was determined in Study I. Eighteen percent (95% CI 16.0-19.9), 11.1% (9.5-12.8), 6.8% (6.5-7.1) and 1.2% (1.0-1.4) had any type of PAD, APAD, IC, and SLI, respectively. The distribution of different stages separated by regions is presented in Figure 5. Karlstad had a significantly higher prevalence of any PAD and APAD compared to other regions (p<.001 and p<.001). The symptomatic stages of PAD (IC and SLI) were most prevalent in Malmö and Älvkarleby regions (p=.08 and p=.008).

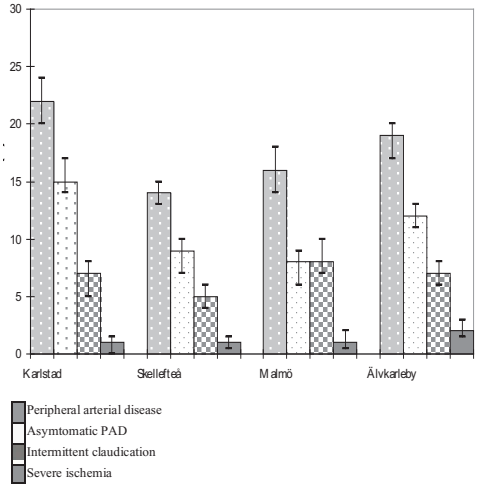

Figure 5. Prevalence of different PAD stages separated by geographic regions in percentages and 95% confidence intervals

The participation rate differed between regions and with ages of the participants. Malmö had significantly more non-participants than the other regions (Figure 6).

A telephone interview was performed among randomly selected non-participants for further characterization of this group. The main reasons for not attending were severe illness or lack of time. Seven percent of the non-participants responded positive to the questions in Rose Claudication Questionnaire, indicating a similar rate of IC prevalence in this group as among participators. The number of included immigrants in Karlstad, Skellefteå, Malmö and Älvkarleby was; 6.8%, 2.8%, 20.4% and 8.8% respectively.

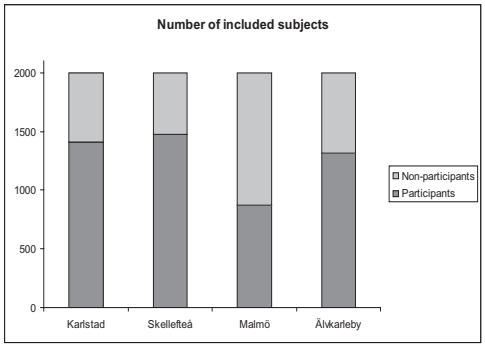

Figure 6. Participants and non-participants at the geographic regions (N)

Table 9. Baseline characteristics of participants with and without PAD (N=4926)

		No PAD (N = 4 056)		PAD (N = 883)		Asymptomatic PAD (N = 553)		Intermittent Claudication (N = 330)		Severe Limb Ischemia (N = 65)	
		Count	%	Count	%	Count	%	Count	%	Count	%
Sex	Woman	2167	53%	525	59%	347	63%	178	54%	45	69%
	Men	1889	47%	358	41%	206	37%	152	46%	20	31%
Age	60-64 years	1098	27%	90	10%	57	10%	33	10%	4	6%
	65-69 years	926	23%	113	13%	75	14%	38	12%	4	6%
	70-74 years	792	20%	128	14%	78	14%	50	15%	4	6%
	75-79 years	634	16%	207	23%	134	24%	73	22%	19	29%
	80-84 years	442	11%	195	22%	119	22%	76	23%	24	37%
	85-90 years	164	4%	150	17%	90	16%	60	18%	10	15%
Region	Karlstad	1078	27%	301	34%	210	38%	91	28%	12	18%
	Skellefteå	1202	30%	196	22%	120	22%	76	23%	14	22%
	Malmö	722	18%	139	16%	67	12%	72	22%	10	15%
	Älvkarleby	1044	26%	244	28%	153	28%	91	28%	29	45%
BMI	Normal weight	1640	40%	383	43%	261	47%	122	37%	27	42%
	Over weight	1660	41%	325	37%	204	37%	121	37%	22	34%
	Obese	591	15%	121	14%	60	11%	61	18%	13	20%
Smoking habits	Non smokers	1981	49%	366	41%	243	44%	123	37%	20	31%
	Smoked < 10 years	547	13%	88	10%	53	10%	35	11%	8	12%
	Smoked 10-30 years	871	21%	153	17%	95	17%	58	18%	18	28%
	Smoked > 30 years	657	16%	276	31%	162	29%	114	35%	19	29%
Cardiovascular disease		1731	43%	555	63%	315	57%	240	73%	50	77%
Diabetes mellitus		352	9%	151	17%	78	14%	73	22%	17	26%
Stroke		239	6%	126	14%	76	14%	50	15%	10	15%

RISK FACTORS FOR PAD

Comorbidities and risk factors present in subjects with and without PAD were evaluated in Study II. The participants with PAD reported several CV morbidities and risk factors. Overall, the more severe the PAD stage, the larger the proportion of subjects with concomitant risk factors (Table 9).

For example, the odds ratios (OR) for reporting smoking, having DM or CAD for the group with the most severe stage SLI were 2.6 (1.3-5.1), 2.7 (1.4-5.0) and 6.3 (3.1-13.0) and 1.2(0.9-1.5), 1.6(1.2-2.1) and 1.9 (1.3-2.9). Smoking was common and 61% were either smokers of former smokers and long time smoking (>30 years) was equally prevalent in the three PAD stages, 32 %. Only 16% of subjects without PAD were long time smokers. Smoking for 10-30 years was more prevalent among SLI subjects compared to APAD- and IC-subjects (28% versus. 17%) (Table 9).

The extent of reported risk factors associated with PAD also displayed regional differences. Significantly ($p<.001$) more subjects reported DM (Figure 7) and were overweight (Figure 8) in Älvkarleby compared to other regions whereas smoking was more prevalent in Malmö.

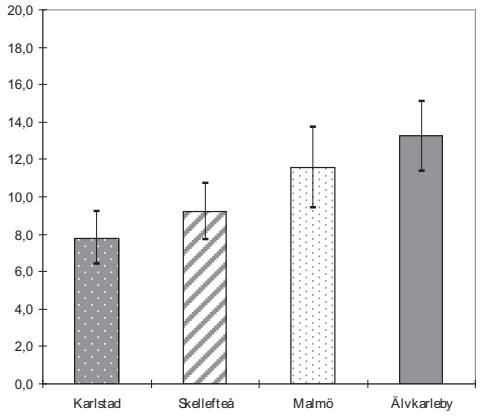

Figure 7. Prevalence of Diabetes Mellitus in different Swedish regions presented in percentages with 95% confidence intervals

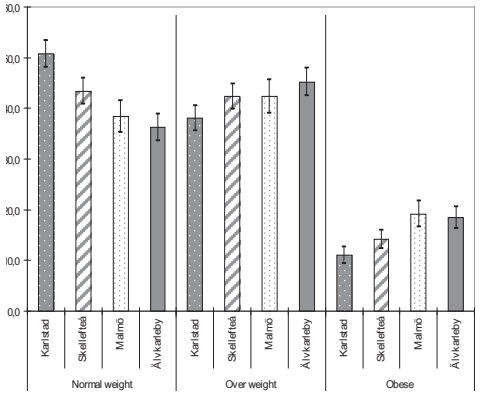

Figure 8. Body-Mass Index with 95% confidence intervals in different Swedish regions

PHARMA COLOGICAL TREATMENT OF PAD

In Study II the use in 2004 of all kinds of medical therapy recorded by the participants is presented. CV preventive medication was of particular interest and treatment rates for lipid lowering, cardioprotection, which included ACE-i and β-blockers, and anti-platelet drugs were 22.6%(22.3-23.09), 47.1%(46.0-43.69) and 37.9%(37.1-38.6), respectively. More preventive medication was used by participants with more severe PAD disease. The part of the APAD subjects, for instance, used lipid lowering, cardioprotection and anti-platelet drugs in 17.9%(17.6-18.1), 42.8%(42.0-43.6) and 31.9%(31.4-32.4) compared to 42.6%(42.5-42.7), 56.6%(56.6-56.7) and 61.8%(61.6-62.0) for SLI subjects. Drug use differed between regions. In Karlstad for example 11.1%(9.5-12.7) of subjects reported use of cardioprotective drugs compared to 6.9%(5.2-8.5)(p=.006) in Malmö. Likewise 12.9%(11.2-15.6) of subjects in Skellefteå used anti-platelet therapy compared to 5.7%(4.2-7.2) (p<.0001) in Malmö.

SEX DIFFERENCES

Sex differences in PAD prevalence was evaluated in Study I and risk factor distribution and drugs analysed in Study II. The prevalence of PAD stages by sex is shown in Figure 9. APAD was more frequent among women (p=.03) than men and so was SLI (p=.008). This pattern was consistent for all age groups. IC prevalence tended (p=.09) to be more common among men. In the oldest age group and for subjects aged 75-79 years, IC had a significantly higher prevalence among men.

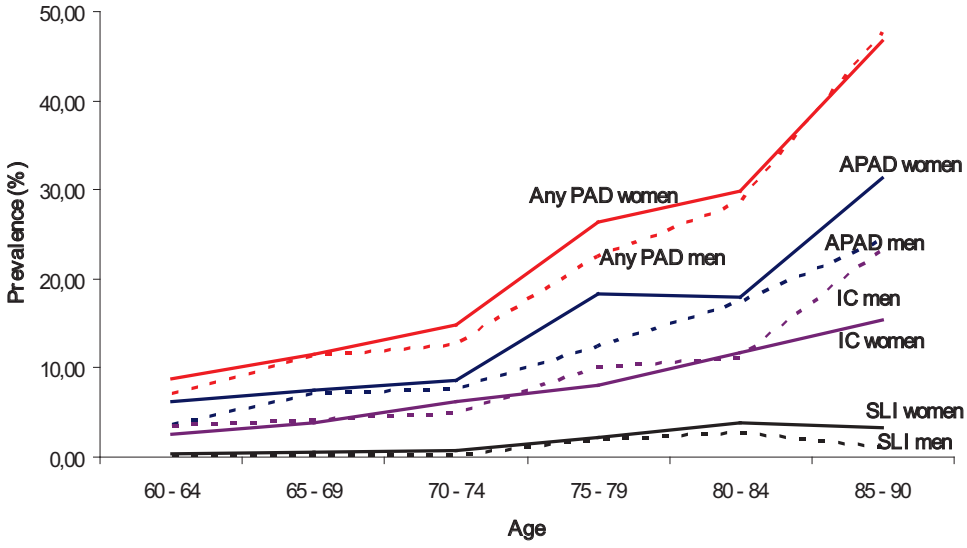

Figure 9. PAD prevalence by age, sex and stage of PAD (Percent)

Risk factor occurrence also differed slightly between the sexes (Table 10). For example, the relationship between the presence of APAD and age appeared already at 66 years among men, whereas this association was not observed in women until the age of 75 years. Significantly ($p<.001$) more women had only PAD compared to men, who in turn reported more isolated CAD and multiple CVD.

Table 10. Relationship between selected risk factors and PAD stages separated by sex (N=4926)

Riskfactors		PAD OR (95% CI)		APAD OR (95% CI)		CI OR (95% CI)	
		Women	Men	Women	Men	Women	Men
Age	*60-64 years*	*Reference category*		*Reference category*		*Reference category*	
	65-69 years	1.5^{NS} (1.0 - 2.2)	1.7^{NS} (1.0 - 2.7)	1.3^{NS} (0.8 - 2.2)	**2.2*** (1.2 - 4.2)	1.9^{NS} (0.9 - 3.4)	1.1^{NS} (0.6 - 2.3)
	70-74 years	2.1*** (1.4 - 3.1)	2.3*** (1.4 - 3.7)	1.8* (1.1 - 2.9)	3.2*** (1.7 - 5.9)	3.0* (1.5 - 6.0)	1.5^{NS} (0.7 - 3.1)
	75-79 years	4.7*** (3.2 - 6.9)	4.4*** (2.8 - 7.1)	4.5*** (2.9 - 6.9)	5.4*** (2.9 - 9.9)	6.3*** (3.1 - 12.7)	3.3*** (1.7 - 6.4)
	80-84 years	5.1*** (3.5 - 8.0)	7.2*** (4.5 - 11.6)	4.0*** (2.4 - 6.4)	9.3*** (5.1 - 17.2)	9.5*** (4.6 - 19.4)	5.1*** (2.6 - 10.0)
	85 years or older	11.7*** (7.3 - 18.5)	16.3*** (9.4 - 28.5)	10.6*** (6.2 - 18.0)	19.0*** (9.3 - 38.8)	17.6*** (8.0 - 38.7)	15.3*** (7.2 - 32.5)
Smoking	*Non smokers*	*Reference category*		*Reference category*		*Reference category*	
	Smoking < 10 years	0.9^{NS} (0.6 - 1.3)	1.3^{NS} (0.8 - 2.1)	0.9^{NS} (0.6 - 1.4)	1.2^{NS} (0.7 - 2.0)	1.0^{NS} (0.5 - 2.0)	2.1^{NS} (1.0 - 4.4)
	Smoking 10-30 years	**1.5*** (1.1 - 2.1)	1.1^{NS} (0.8 - 1.7)	**1.7**** (1.2 - 2.4)	1.0^{NS} (0.7 - 1.6)	1.3^{NS} (0.7 - 2.3)	1.5^{NS} (0.8 - 2.7)
	Smoking > 30 years	3.8*** (2.8 - 5.2)	4.3*** (3.1 - 6.1)	3.6*** (2.5 - 5.1)	**3.4***** (2.3 - 5.0)	5.4*** (3.3 - 8.8)	**6.3***** (3.6 - 11.0)
Weight	*Normal weight*	*Reference category*		*Reference category*		*Reference category*	
	Over weight	0.9^{NS} (0.7 - 1.1)	0.9^{NS} (0.6 - 1.1)	0.9^{NS} (0.6 - 1.2)	1.0^{NS} (0.7 - 1.5)	1.2^{NS} (0.7 - 2.2)	1.0^{NS} (0.5 - 1.7)
	Obese	0.9^{NS} (0.6 - 1.2)	1.0^{NS} (0.6 - 1.5)	0.8^{NS} (0.5 - 1.2)	1.3^{NS} (0.7 - 2.5)	1.9^{NS} (1.0 - 3.8)	1.0^{NS} (0.4 - 2.7)
Region	*Älvkarleby*	*Reference category*		*Reference category*		*Reference category*	
	Karlstad	0.9^{NS} (0.7 - 1.2)	1.1^{NS} (0.8 - 1.6)	1.0^{NS} (0.7 - 1.3)	1.0^{NS} (0.7 - 1.6)	0.7^{NS} (0.4 - 1.1)	1.3^{NS} (0.8 - 2.2)
	Skellefteå	0.6*** (0.4 - 0.8)	1.2^{NS} (0.9 - 1.8)	0.5*** (0.4 - 0.8)	1.1^{NS} (0.7 - 1.7)	0.6* (0.4 - 1.0)	1.5^{NS} (0.9 - 2.5)
	Malmö	0.5*** (0.3 - 0.7)	1.1^{NS} (0.7 - 1.7)	0.3*** (0.2 - 0.6)	1.0^{NS} (0.6 - 1.6)	0.8^{NS} (0.4 - 1.3)	1.2^{NS} (0.7 - 2.2)
Diseases	*No disease*	*Reference category*		*Reference category*		*Reference category*	
	Diabetes mellitus	1.5* (1.1 - 2.1)	2.4*** (1.7 - 3.4)	1.4^{NS} (1.0 - 2.2)	1.8* (1.2 - 2.9)	2.2* (1.2 - 4.0)	3.4*** (1.8 - 6.4)
	CAD	1.8** (1.2 - 2.8)	**2.2***** (1.5 - 3.3)	2.1* (1.1 - 3.7)	2.3* (1.2 - 4.2)	2.8*** (1.8 - 4.3)	2.2** (1.4 - 3.5)
	Congestive heart failure	1.2^{NS} (0.7 - 2.2)	1.1^{NS} (0.4 - 3.0)	2.7* (1.1 - 7.1)	1.0^{NS} (0.2 - 5.1)	1.2^{NS} (0.5 - 2.6)	2.7^{NS} (0.9 - 8.5)
	Hypertension	1.6*** (1.2 - 2.0)	1.7** (1.2 - 2.4)	1.6** (1.2 - 2.2)	1.5^{NS} (1.0 - 2.2)	2.0* (1.1 - 3.4)	2.6** (1.4 - 4.8)

NS = No significance

* 0.05 > p-value > 0.01

** 0.01 > p-value > 0.001

*** p-value < 0.001

The main differences in smoking habits were that smoking appeared as a risk factor for women already after 10 years of smoking, as compared with 30 years for men. Non smoking rates were 57.5% for women as compared with 35.9% for men. Long time smoking (10-30 years) was more common among men than women (26.4% versus 15.9%). This is presented in Figure 10.

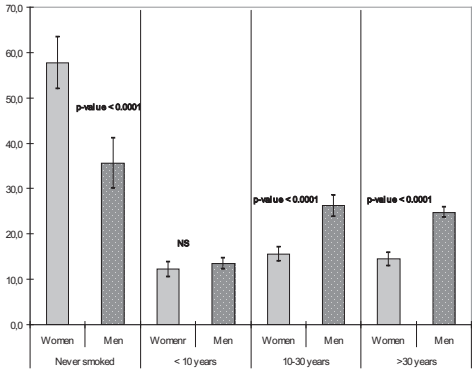

Figure 10. Prevalence (95% confidence intervals) of smoking habits in the total cohort (n=4926) (p values according to test of equal proportions comparing men and women, NS; equals not significant).

Use of drugs with a potential of preventing CVD was more common among men than women (p<.0001 for all PAD stages and drugs, with two exception Figure 11).

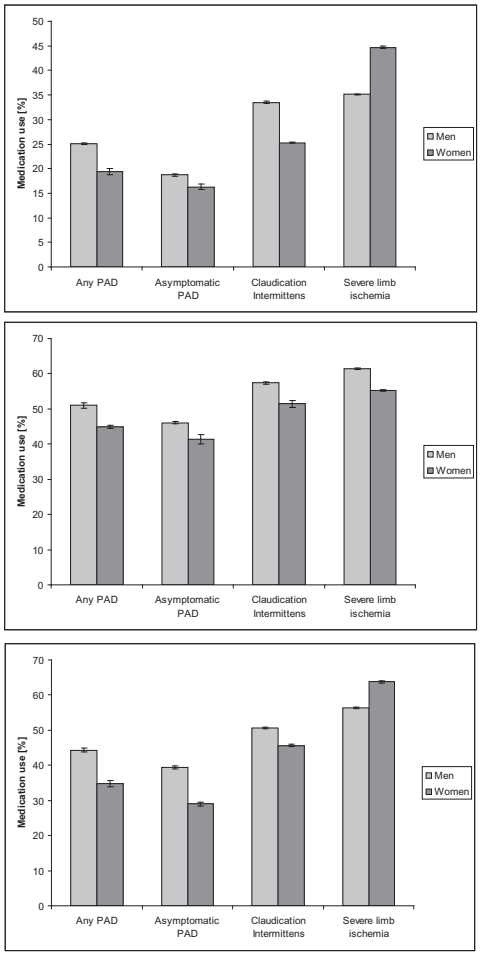

Figure 11. Medication use among men and women with different PAD stages in percentages with 95% CI (A, Lipid lowering therapy. B, CV prevention therapy. C, Anti-platelet therapy).

DIAGNOSING INTERMITTENT CLAUDICATION IN EPIDEMIOLOGICAL STUDIES

In Study III the problem of diagnosing IC was evaluated. Data comes from SPPS as well as a separate follow-up study. Women in the IC cohort in SPPS had a tendency to report a worse walking ability, according to the WIQ score (distance p=0.1, speed p=0.01 and stair climbing p=0.1) compared to men. This difference was significant for the other PAD cohorts as well as for the subjects without PAD in SPPS. Women with IC also had more symptoms reflecting other problems that may interfere with walking ability such as ache in joints, chest pain and heart palpitation (p=.02, p=.06 and p=.001) (Figure 12). The mean ABI among IC subjects was 0.7(SD.2). A fifth (19%) of women with IC had ABI<0.5 compared to 7% of the men.

The follow-up cohort consisted of 56 (35 women) subjects of SPPS participators with IC (Figure 3). In this group women reported numerically (but not significantly) more pain in joints and they more often had HTN than men. Men reported CAD and DM to a larger extent. ABI had decreased for men and women from 0.67(SD. 0.13) and 0.69(0.15) to 0.44(0.39) to 0.44(0.40) (p<.0001) during the 4 years between SPPS and follow up. Compared to initial measurements men deteriorated more in all WIQ domains than women. Walking ability and distribution of atherosclerotic lesions were similar in men and women. In the echocardiography heart function studies women had a tendency (p=.06) to display better values than men (EF 41.2% versus 15.4%). In the interview, men presented classic IC symptoms more frequently than women who in turn described atypical symptoms as tiredness, numbness and unsteadiness.

A summary of results from Study I-III from a sex perspective is given in Table 11.

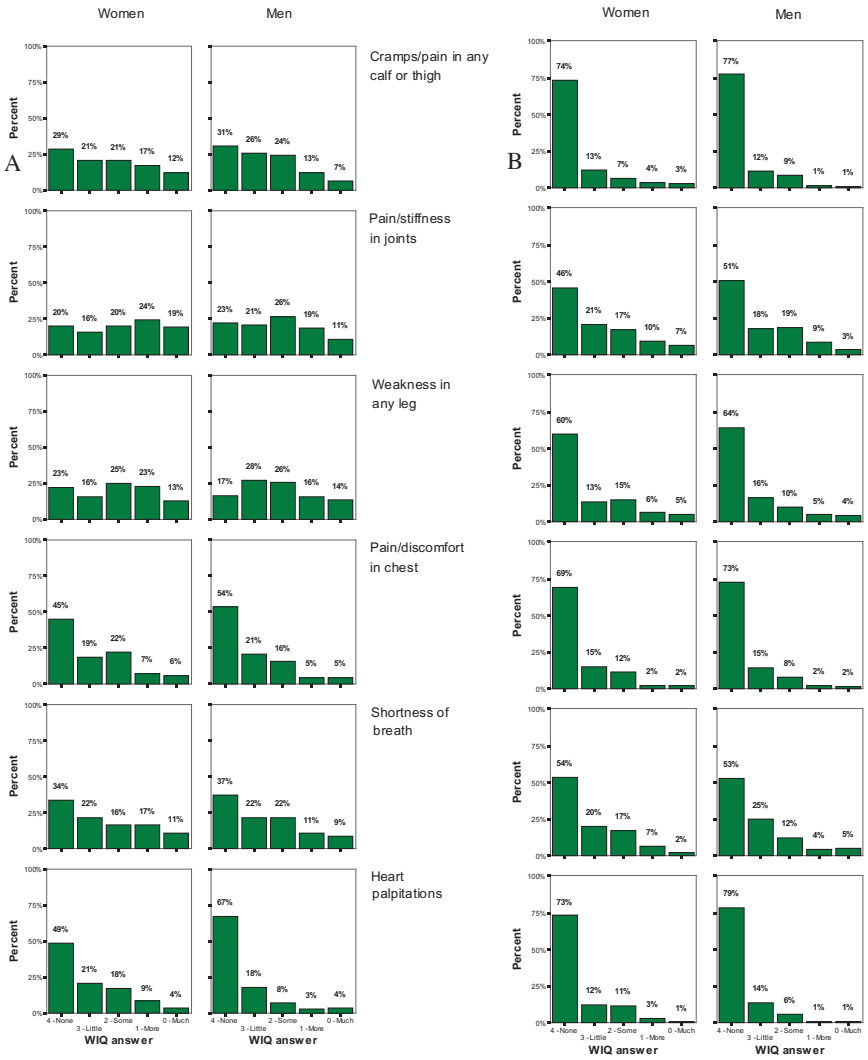

Figure 12. The Walking Impairment Questionnaire scores of symptoms limiting walking ability in SPPS separated by sex.

(100= no difficulties, 0=unable). A, Subjects with Intermittent Claudication. B, Control subjects.

Table 11. Summary of results from Study I-III from a sex perspective.

		Women	Men
Prevalence of:	any PAD	+	
	APAD	++	
	IC		+
	SLI	++	
	Diabetes mellitus		++
	Stroke		+
	Hypertension	No difference	
	CAD		++
Smoking	<10 years	No difference	
	>10 years		++
	10-30 years		++
Use of	lipid lowering drugs		++
	cardio protective drugs		++
	anti-platelet therapy		++
Lowest ABI	initial survey	No difference	
	follow-up	No difference	
Pathological lesion by DUS		No difference	
Lowered EF			+
Distance 6MWT		No difference	
Walking Impairment Questionnaire			
Weakness in leg			
	Controls	++	
	Positive Rose	++	
	IC subjects	No difference	
Pain, stiffness in joints			
	Controls	++	
	Positive Rose	++	
	IC subjects	++	
Heart palpitations			
	Controls	++	
	Positive Rose	++	
	IC subjects	++	
Walking speed (lowest)			
	Controls	++	
	Positive Rose	++	
	IC subjects	+	
Walking distance (shortest)			
	Controls	++	
	Positive Rose	++	
	IC subjects	+	
Intermittent Claudication Questionnaire			
Pain limiting walking 100 meters		+	
Pain limiting leaving house			+
Time spent thinking of leg pain		+	
Felt down-hearted because of pain			+
Interference with work			+

+=Numerical differences
++=Significantly differences

COST-EFFECTIVENESS OF PHARMACOLOGICAL RISK PREVENTION IN APAD

Study IV aimed to clarify if early drug prevention in PAD is cost-effective and all four drugs evaluated in the model reduced CV events. ACE-i resulted in a hazard ratio (HR) of 0.67 (95%CI 0.55-0.79), statins of 0.74 (0.70-0.79), and clopidogrel of 0.72 (0.43-1.00). Aspirin had a HR of 0.87 and the 95%CI passed one (0.72-1.03). Accordingly, ACE-i was associated with the largest reduction in CV events. ACE-i was also associated with a lower total cost than aspirin and clopidogrel, but a higher cost compared with statins (Table 12).

Table 12. Estimated health outcome and costs in a simulated cohort of APAD over a life time

	Clinical practise		ACE-i		Statins		Asprin		Clopidogrel	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Angina Pectoris	0.143	0.157	0.133	0.148	0.135	0.150	0.139	0.153	0.135	0.149
Stroke	0.151	0.165	0.140	0.155	0.142	0.157	0.147	0.162	0.142	0.157
Myocardial Infarction	0.159	0.173	0.146	0.162	0.149	0.164	0.154	0.169	0.148	0.146
CV death	0.218	0.249	0.223	0.257	0.222	0.255	0.220	0.252	0.222	0.256
Mean life years	11.39	12.82	11.47	12.89	11.46	12.88	11.42	12.85	11.46	12.88
Mean Utilities	7.42	8.46	7.50	8.53	7.49	8.51	7.45	8.48	7.49	8.51
Mean costs (€)	38.015	43.752	37.831	43.533	37.806	43.513	37.986	43.710	41.150	47.033

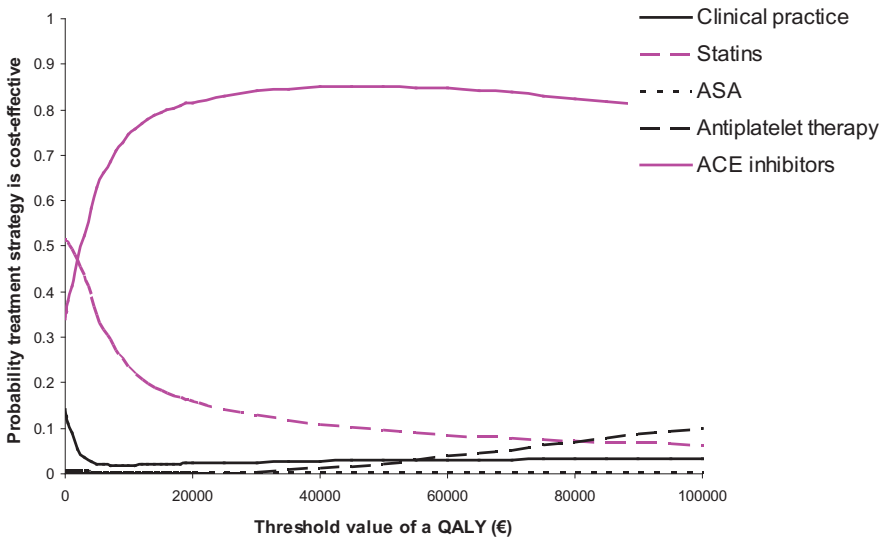

Figure 13. Cost-effectiveness acceptability curves

The cost per QALY gained for ACE-i compared with statins was far below conventional threshold values for cost-effectiveness. The probability that ACE-i is cost effective is 25%, if the willingness-to pay is 0 €. If the threshold is 20.000 €, the probability of ACE-i being cost-effective is 85% (Figure 13).

In summary, the studies performed in this project have revealed the PAD is common among elderly, and especially in women. Risk factors occurring with PAD are the known ones but a substantial number of the subjects have only PAD and do not report smoking habits or are medicating to modify their high CV risk. Diagnosis of IC is a particular problem in epidemiological studies, and the prevalence of this PAD stage may therefore be underestimated in women. ACE-i may be the drug of choice for early prevention of CV risk in PAD, and the benefits of aspirin may be overrated.

DISCUSSION

The purpose of epidemiology is to provide reliable information of burden and cause of health problems in a population in order to enable changes that decrease risk and improve health. CVD is common in most populations and is associated with mortality, loss of independence, impaired HRQL, social and economic costs. The epidemiologic research of the past several decades has advanced understanding substantially. In CAD, for example, epidemiological research has had a huge impact whereas in PAD it needs to be developed through further research. There is a global public health challenge of addressing PAD as it provides an opportunity for effective public health action.

This thesis shows that PAD is common and to a large extent unknown and unattended. Almost one fifth of elderly individuals have some stage of the disease and women are more often afflicted than men. IC is probably underdiagnosed and undertreated in women, both in general and perhaps even as an indication for revascularization. It is probable that current prevention policies are not up to-date and even if they were it is probable that they not are implemented sufficiently. The latter can be the case either at the population or the individual level, and it is likely to be a special problem for women. Though costs are associated with medication, our findings suggest beneficial effects for society and individuals of preventive drugs treatment for subjects with subclinical PAD. New updated guideline recommendations are needed in this area.

IS PAD PREVALENCE ESTABLISHED?

Despite the abundance of epidemiological studies on PAD, its true prevalence is not firmly established for all aspects of this disease. Before our study SPPS (Study I) there were, with one or two exceptions, no data on CLI prevalence and little information was available in the literature about sex differences [147]. IC male cohorts have been widely assessed. Moreover, the true IC prevalence is unreliable with prevalence data varying from 1%-14% [51, 65, 66, 69]. We believe that SPPS provide accurate and up to date information on prevalence for all PAD stages that is relevant for both sexes. Our results indicate that PAD is common in the older age groups and most subjects are asymptomatic. SPPS adds new information on CLI and female PAD occurrence, and provides data that can be used for future health care planning in this field. The prevalence of CLI determined to be between 0.4 to 1.4 percent of the elderly population needs to be confirmed by additional studies, but if it is at this level vascular surgical resources need to be increased [148]. Similarly, it appears as PAD is more common in women than what is reported in the literature. For example Diehm et al showed that the prevalence of IC was 2.3% compared to our current data of 6.5% (Study I) in a similar age group [25]. This information prompted our further research efforts to clarify why the female dominance not is the case for IC. If women are more prone to develop PAD or if this is an effect of a diagnosis related sex differences and risk this must be examined.

TEMPORAL TRENDS IN PAD PREVALENCE

The question whether there are temporal changes in PAD prevalence is important to pose because it may be a way to evaluate the effects of preventive programs. It is also of importance when trying to plan for health care resource allocation. A comparison of our data (Study I) with those reported in the Rotterdam study [52] that was performed in the 90:ies, suggests a rather constant PAD prevalence over this 10 year period. This is contradicted by Fowkes et al's findings that were published in 1991. This study found a higher prevalence than in SPPS for comparable age categories, indicating a decline in prevalence over time. Temporal trends of PAD prevalence in Sweden can be estimated by comparing our data with a study published by Skau et al in 1993. This report executed a population-based study in a Swedish community in the early 80:ies and enrolled men and women aged 50-89 years. A comparison with our data shows a similar prevalence reported for symptomatic PAD in younger age groups, but a far lower one among elderly (13% versus 5%) in that study [69]. The reason for this discrepancy is unclear, but it is likely that a better CV risk prevention has contributed.

If all these observations are valid it suggests that risk-reducing measures that were implemented in the late 80:ies had a clear effect on PAD development but little has happened the last decade. More aggressive strategies in order to further reduce the risk for developing PAD may thus be needed. Variations in study design, dissimilarities between countries, ethnic groups and risk factors can of course also be plausible explanations for the differences in prevalence observed. One has also to keep in mind that in absolute numbers the proportion of elderly with PAD is likely to increase due to longer life-expectancies. It has increased in the western world with 30 years since the year 1900 and is expected to continue to do so. For example, a majority of children born 2000 will celebrate their 100 birthday [149]. A forecast of PAD prevalence in Sweden is presented in Figure 14, assuming a stable incidence of PAD and an increasing proportion of the population attending older age. Accordingly, in the next decade almost half a million Swedish elderly will have PAD.

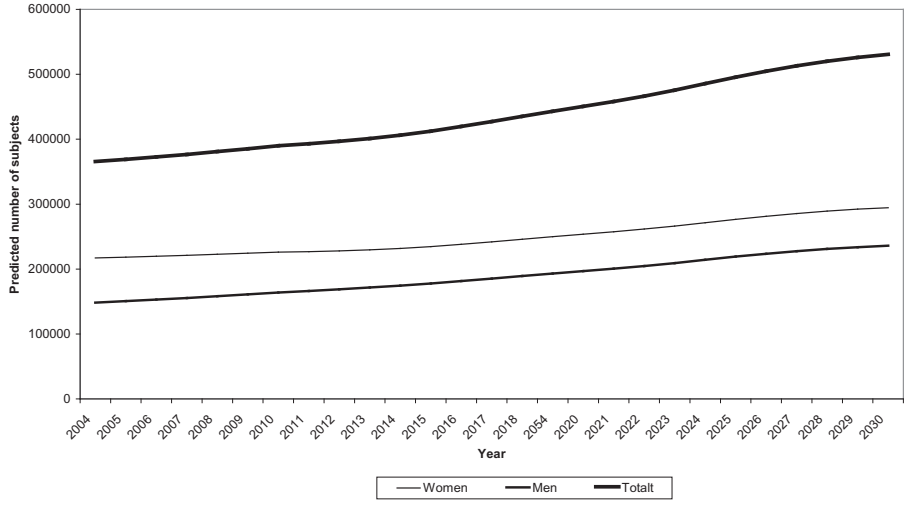

Figure 14. Prediction of number of subjects with PAD in Sweden year 2004 – 2030.

Data based on prevalence rates in SPPS and demographics by The Council of Official Statistics in Sweden

It is also probable that PAD prevalence will increase in less developed countries. According to WHO, CVD has become far more prevalent in such countries than previously thought, and CV mortality rates in India, South Africa and Brazil are 1.5-2 times higher than those in the US currently. Even if nothing changes in the next 30 years, population growth alone will lead to major increases in CVD in developing countries and it is concluded to be a "public health time bomb" if too little is done to reverse the trend [64]. This development also suggests a sharp increase in PAD prevalence world wide in the future.

In summary, it is much to suggest that PAD prevalence is constant over time, but with a changing demographic profile, the numbers of patients with PAD are likely to increase in the future. Alterations in risk factor occurrence may influence development. Achieving this is challenging for health care workers, who need to convince policy makers and politicians of the need for commitment, development and implementation of policies for prevention.

DIAGNOSIS OF PAD

Diagnosing the disease of interest correctly is extremely important in epidemiological studies but this task has been proven difficult in PAD. This statement is not only valid for CLI, as has been discussed previously (page 20), but also for APAD and IC.

Ankle Brachial Index

The diagnostic tool for determining APAD, ABI, is rather well-established but some questions remain. One example is the controversy whether to use the lower or the higher ankle blood pressure from the two ankle arteries. The TASC document recommends use of the highest ankle blood pressure and American Heart Association guidelines does not specify whether to use the higher or lower of the two [2, 146]. ABI calculations presented in epidemiological studies are inconsistent. Some investigators assessed nothing more than the pressure in the posterior tibial artery and used this value [139, 150] either used the mean systolic pressure of the two arteries [151] and some the highest value measured [25]. The results from these studies are therefore not comparable, and the optimal method for PAD detection using ABI needs to be determined. We believe that the lowest ankle blood pressure increases the sensitivity to detect PAD for epidemiological studies, particularly in APAD subjects, and have used this method in this thesis. Another issue is how very high ABI values should be managed. It is well known that DM patients have falsely elevated ankle BP due to incompressible arteries, and thus likely to have ABIs >0.9 and being categorized to not having PAD [139, 152]. In most epidemiological PAD studies the same ABI criteria are used for DM and patients without diabetes, but in a recent clinical trial the cut of value for having APAD in DM was raised to 0.95 [153]. A third problem concerns if different cut off values should be used for men and women. Healthy men are known to have a higher average resting ABIs compared to women, possibly explained by men being taller [154]. This raises the question if different ABI levels should be used for men and women for PAD diagnosis. Differentiating reference values for measurements of biochemical analysis, weight and length etc according to sex is standard procedure, but despite of differences in height that possibly may influence hydrostatic pressure the same cut-off values used for ABI in men and women.

Accordingly, different ABI criteria for PAD may alter sex differences in PAD prevalence. These questions needs to be clarified in future research,

and may significantly influence APAD prevalence data.

Intermittent Claudication

For IC there are several options for diagnosis depending on whether the perspective is strictly clinical or for use in public health studies. Also in epidemiological studies diagnostic criteria differ. The WHO/Rose Questionnaire was developed 1962 and is widely used, including in Study I in this thesis. It has a high specificity (90-100%) but is only moderately sensitivity (60-68%) for diagnosing IC as defined as leg pain during ambulation. The characteristics of the original definition included [155]:

1. Its site must include one or both calves.
2. It must be provoked by either hurrying or walking uphill.
3. It must never start at rest.
4. It must make the subject either stop or slack in pace.
5. It must disappear on a majority of occasions in 10 minutes or less from the time when the subject stands still or rest.
6. It must never disappear while walking continues.

The Edinburgh Claudication Questionnaire was intended to improve the poor sensitivity by adding questions covering differential diagnosis and was reported to achieved a sensitivity of 91.3% (88.1-94.5%) [156]. These results were later challenged by Bendermarker et al, who reported a sensibility of only 56.2% using only ECQ in a cohort of 4527 in patients that earlier were diagnosed with ABI and medical history by GPs [157]. This may indicate that ECQ alone is inadequate for diagnosis of IC. To further characterize patients' walking impairment and their HRQL the WIQ and ICQ can be useful tools [134] [132]. In this thesis we have employed these instruments in Study III. Our results presented are in a general sense similar to what is published in the literature, but it is also apparent in the WIQ data that there is a clear sex difference even in healthy subjects on how walking problems are reported. This is to our knowledge not described previously.

Therefore, the variation in IC prevalence in men and women is likely to be an effect of difficulties to asses walking problems by questionnaires, and may partly be explained by differences in diagnostic methods and subjective walking demands and interpretation of symptoms (Study III).

Critical limb ischemia

For CLI epidemiological surveys are extremely scarce and new methods need to be developed to enable diagnosis of this PAD stage [158]. Prior attempts are either estimations from registry data [159], questionnaire data based, management of CLI [160] or, as in our study a combination of ankle blood pressure and questionnaire data (Study I and II). Overall better evaluation of the diagnostic tools used in epidemiological research of PAD is needed.

SEX DIFFERENCES

Atherosclerosis

One of the aims of this thesis was to determine if there are sex differences in PAD prevalence and the clinical presentation of PAD. As presented previously our data indicate that this is the case (Study I –III). It appears that PAD is more common in women (Figure 9), but it is unclear why. There may be a difference in distribution of atherosclerotic lesions in men and women which is supported by clinical and autopsy studies. Men have a heavier atherosclerotic burden compared to women and may thus die at earlier age not living long enough to develop PAD [161]. Kardys

et al, for instance, recently noted more disease among men with coronary calcifications (ratio 8:1 for men and women), intima-media thickness in carotid plaques (3:1) but similar frequencies of lowered ABI [162]. This pattern of sex differences in comorbidities and risk factors are apparent also in the studies of this thesis as in another cohort [163]. Men display a stronger association with CAD and stroke, which is in concordance with the differences in distribution of atherosclerotic burden.

According to the literature and our data, the higher PAD prevalence in women does not appear to be an effect of disease distribution.

Sex hormones

Another possibility is that protective effects of estrogens play a role for developing PAD. This question is widely debated and any CV disease preventive effect of supplementary estrogens are not proven in large randomized trials [58, 164]. The Nurses'Health Study investigators have reported that,the post-menopausal increase in CVD risk that occurs is most likely due to age and not to menopause, and the increased risk in women after oophorectomy may be due to confounding by other risk factors [165]. Increased arterial stiffness is found at an earlier age in men than women and this may make them more prone to develop PAD in particular. After menopause the process evolves in a similar way for women [166] and this may contribute to the later onset of CVD among women. It is possible that endogenous adaptation of the vasculature during the period of atherosclerosis progress is more efficient and women therefore develop symptoms later in life and more often have subclinical disease.

Perception of symptoms

There are other sex difference not necessarily related to disease manifestation and risk factors. Women perceive PAD symptoms differently from men when they eventually develop (Study III) [56, 167]. Plausible explanations are that older women with IC do not complain of leg symptoms because they accept walking difficulties as a part of the normal aging process. They also appear to seek medical care more scarcely than men. This is reflected by the difference in treatment frequencies between the sexes for IC. In Sweden are men more likely to be intervened for IC while the opposite is reported for CLI [72] . The main reason why more women than men are undergoing revascularizton for CLI may be the higher female prevalence and the fact that there are more women than men in the very elderly age group where CLI is most common. Furthermore, while IC symptom severity is matter of subjective judgement, CLI symptoms are more severe, often consisting of ulcers and gangrene, and cannot be ignored.

Elderly women and men also appear to live their lives under different circumstances. Women are more physically inactive and engaged in in-door household chores to a larger extent than men (Study III) [168, 169]. They therefore may have few demands on physical performance.

RISK FACTORS ASSOCIATED WITH PAD

Identification of subjects with PAD can be used as a way to detect subjects at high risk for developing PAD. Besides diagnosis issues and sex differences in disease patterns risk factor occurrence is also important to consider. Not all PAD subjects have concomitant CV diseases and would thus remain unrecognized if PAD not is diagnosed. In fact there might be a misconception that PAD always is associated with other CVD. In SPPS 13% of women and 8% of men categorized to having PAD didn't have any known risk factor or concomitant disease (Study II).

Smoking

Surprisingly, 40% of PAD subjects in SPPS claimed to be life-time non-smokers. Considering the general belief (at least up until recently) of PAD as a "smokers' disease" rather than one of aging this information may influence awareness of PAD. Non-smoking frequencies appears to be similar in Germany (46%) [25] but lower in France (30%) [170]. Furthermore, we found no association between having PAD if male subject had smoked for less than 30 years in the SPPS cohort. There are hypotheses proposed in the literature that smoking predisposes to PAD and CAD in different ways. One is the existence of a "threshold phenomenon" in the pathogenesis of PAD. It implies that higher dosages of tobacco smoke are required to develop atherosclerosis in lower limbs than in the coronary circulation [171]. On the other hand, there seems to be a sex difference in the sensitivity to tobacco exposure, as women seem to be more at risk than men (Study II). The same observation is also reported for CAD. In one study, for example, smoking increased the risk for CAD 6-fold for women but only 3-fold for men [39]. Female smokers may also have an increased risk for arterial thrombosis [172] and lipid abnormalities. They also have lower relative levels of HDL compared to non-smoking women [173].

Women's sensitivity for tobacco smoke may have a huge impact on PAD epidemiology. Swedish women were early adapters of smoking habits in the 1960ies and Sweden was the first country in the world where more women than men smoked [174]. In age groups 16-64 years women are twice as likely to smoke compared to men, while men in the older ages is still dominates among current smokers [128]. This is in contrast to third world countries [175]. Taking into account the increased sensitivity for female smoking and the changing smoking habits, smoking may induce PAD development in a sex dependent manner. In the future smoking habit trends may spread to developing countries. One study estimated that approximately 70% of the 10 million tobacco–attributable death expected in 2030 will take place in low and middle-income countries [175].

Other risk factors

Having IC was strongly associated with DM and being obese in the SPPS cohort (Study II). This finding may be due to overreporting of leg symptoms among DM patients with neuropathy or a higher awareness for CVD in DM patients among physicians. Obesity can also be a consequence of an impaired ability to exercise by walking. The relationship between obesity and PAD is known in the literature [176] and obesity also predicts a poor prognosis for PAD symptoms. Over 30 years, BMI and waist circumference have increased [177] and physical inactiveness is a general trend. For example only 25% of children and adults are reported to be enough physically active today [64] and there is data suggesting that health benefits of leanness are limited [178]. The beneficial effects of physical activity for PAD are proven in a various epidemiological studies. Being physically inactive as a PAD patient is associated with the same increased risk for CVD as untreated high blood pressure or hyperlipidemia and ongoing smoking [179].

PREVENTION OF CV EVENTS AND PREVENTIVE MEDICATION

When PAD is diagnosed the most important imperative is to prevent CV events, but it is a matter of discussion whether drug prevention is mandatory. There are many life style modifications that may reduce this risk and some of these have been discussed previously in the thesis (page 25). When these measures are unsuccessful or insufficient and additional measures are required, risk

reduction with drugs should be considered [133, 153, 180]. It is well known that preventive medication can reduce progression of atherosclerosis and the number of clinical events in CVD [4, 181].

PAD unawareness

Despite the fact that there maybe patophysiological differences between PAD and other CVD most guideline recommendations on drug prevention are based on extrapolations from general high-risk population and CAD outcome studies. Several studies report lower use of statins, antiplatelet agents and anti-HTN drugs in PAD patients compared to CAD and there is little change over time in this pattern. The OR for PAD subjects taking anti-platelet drugs and statins compared to CAD subjects were reported to be 0.53 and 0.48 respectively in a survey carried out 2004. This is in concordance with older data from 1997. CAD subjects were twice as likely as PAD subjects to use CV preventive medication [170, 182]. Also in SPPS only a minority of PAD subjects used preventive medication (Study II). From a societal perspective this implies a continued need for improvement in pharmacological drug prevention to reduce CV morbidity and mortality in PAD. The reason why PAD subjects not are offered medication is unclear, but there seem to be several hampering obstacles. Diverging guidelines, physician's unawareness of PAD, including the possibility of using a lowered ABI as a marker of CVD may be the most important ones. Cost of treatment is also likely to play a role.

One example of the unawareness is the sex difference. Data from Study II suggests a much lower use of preventive medication among women compared to men. Despite a similar calculated risk for women and men, physicians' insight of the high risk women with PAD face may be a primary factor associated with the implementation of preventive measures. If this is low it may explain sex differences in prescription of preventive drugs [183]. Another barrier for medical CV protection with drugs is disease awareness among women themselves. Only a small percentage of them believe that CVD constitute to the greatest threat to their health [56]. Breast cancer claims only one-tenth of women's lives as compared with CVD, but it is often reported by media being leading cause of morbidity and mortality.

The regional difference in drug use observed in Study II is another example. We found differences in risk factors and drug use between the including regions in SPPS and this may be explanatory for the displayed variation in PAD prevalence. Swedish registers for MI and stroke have pointed out similar geographic dissimilarities [184, 185]. Another factor may be an anticipated low adherence to the prescribed preventive drugs. The reasons for not-prescribing can be divided into patient and physician-attributed factors, some patients do not adhere to prescribed and agreed medication and others object to taking medication, partly for legitimate reasons such as expected or perceived side effects. Furthermore, physicians themselves may have doubts for prescribing medication in patients with short life expectancy, expected compliance problems or near "goal levels". Finally, barriers in health organisation within primary-secondary care may interfere.

Drug prevention in APAD

One question is if APAD subjects have the same risk as symptomatic subjects and therefore should be diagnosed and treated. Having APAD in SPPS was associated with most common risk factors while subjects not having PAD were not (Study II). This is a consistent finding also in other reports [5, 6, 92]. Further on is beneficial treatment effects suggested being similar between the

groups [186], explained of, whether symptoms appear or not, is an effect of the extent and location of atherosclerotic plaques and walking needs for at least IC. We believe that risk reduction would be equally beneficial in all stages and the diverging guideline recommendations for primary prevention of CV risk in APAD subjects are probably an effect of lack of data.

It is well known that resources are limited and cost and cost-effectiveness is important for prescription patterns [187, 188]. In Study IV we found that it is cost-effective to treat APAD. All four drugs resulted in an event reduction compared with clinical practise. ACE-i and statins had better effect to a lower cost than the other drugs. ACE-i treatment was associated with the largest reduction in CV events leading to the highest QALYs. Aspirin treatment was associated with a low mean cost but also a small event reduction. These findings are in direct contrast to what is recommended in prevention guidelines (Table 5). They support use of aspirin and rarely mention ACE-i for in PAD patients.

WHAT IS THE OPTIMAL TREATMENT STRATEGY FOR RISK REDUCTION?

The management of PAD patients is challenging because the limited high-quality data available to guide an optimal treatment strategy. The goal is to reduce CV risk, improve symptoms of IC, and prevent progress to CLI and amputation. The first task is to identify subjects at risk. Several risk scores for identification has been tried but shown to have a limited accuracy. Most tend to overestimate risk in low-risk population and vice versa [180, 189]. Biochemical risk markers have also been introduced but rarely improve prediction of high risk [190]. Diagnosing PAD on the other hand, is a simple way to identify high CV risk subjects. A lowered ABI indicates generalised atherosclerosis [139, 163, 191] and detecting subclinical PAD with ABI measurement is a potential useful tool to identify subjects with high CV risk. This test is cheap, quick and easy to perform with a high sensitivity, sensibility and validity [85, 192].

Drug prevention

The next step is to consider treatment options. Providing that life style modifications are implemented there are some drug options to consider. The ones promoted in guidelines for PAD have already been mentioned above and are anti-platelet therapy (including aspirin and clopidogrel), statins and anti-HTN.

Aspirin was used by 38% of all PAD subjects in SPPS (Study II). It is considered the cornerstone of medical PAD treatment among most vascular surgeons and angiologists [181, 193, 194]. This is rather odd considering the lack of scientific evidence for its use in this patient group. In fact there is only one single randomized trial supporting its beneficial effects [110]. We showed, as discussed above, that aspirin probably not is cost-effective in APAD, by large a consequence of its very limited risk reducing effect (Study IV). A still not published study was reported by Fowkes et al at the European Society of Cardiology meeting in 2009 support our findings [195]. In this study subjects were followed for a mean 8.2 years and no reduction in the number of CV events (HR 1.03, 95% CI 0.84- 1.27) was found with aspirin. A large increase in major haemorrhages and gastrointestinal ulcers in the aspirin patients group was noted instead (2% versus 1.2% for placebo and 0.8 % versus 0.5% for placebo respectively).

Accordingly, beneficial effects of aspirin treatment for prevention in PAD subject are questionable and even unlikely for APAD. In our cost-effectiveness analysis aspirin treatment gained

the lowest mean QALYs compared with other treatment strategies. These findings are in direct contrast to what is recommended to day and emphasizes the need for a review of the current guidelines.

Due to their pleiotropic effects, ACE-i and ARBs have shown clinical benefits independent of blood pressure lowering [118]. HOPE study findings support CV event reduction in all PAD stages, even APAD [120]. Our cost-effectiveness analyses noted the largest event reduction (HR 0.67) for ACE-i compared to other drugs (Study IV). Furthermore, it is possible that ACE-i treatment has a positive effect on walking distance in IC patients [196]. These findings should be enough for promoting higher prescription rates of ACE-i for all PAD patients.

Twenty-three percent of subjects with PAD in SPPS were on statin therapy (Study II). Statins prevent CV events regardless of cholesterol values in high-risk CVD patients [112] and improve leg symptoms in patients with IC [115, 116] and reduces rates of revascularization procedures [197]. From a health economic perspective statins are likely to be cost-effective for treatment of APAD subjects, even though the QALY gain was lower than for ACE-i in our model (Study IV). These findings are not supported by current guidelines where dietary treatment is recommended as first line therapy for dyslipedemia and statins saved for achieving of target lipid levels when not reached (Table 5).

A recent published systematic appraisal of the literature suggests that three major CV therapies are beneficial in patients with symptomatic PAD. The estimated pooled risk reduction for MI, stroke and CV death was for anti-platelet agents 26% (95% CI 10-42), statins; 26% (18-33) and ACE-i; 25% (8-39) and the estimated cumulative relative risk reduction for all three strategies was 59% (32-76). Population level analyses suggest that secondary vascular protection could prevent more than 200.000 events in patients with PAD each year [198]. There are also available data of these drugs being cost effective [199-201]. The merits of primary prevention strategies for CVD are less clear, in particular for PAD.

In summary, the best treatment for PAD subjects consists of smoking cessation, physical exercise and pharmacological prevention. Treatment with ACE-i and statins should probably be initiated in all PAD subjects. Evidence of beneficial effects of aspirin seems to be ambiguous

HOW CAN WE IMPROVE PAD AWARENESS?

Given that that there is agreement about CV prevention and treatment of symptoms in PAD, better awareness is warranted. One goal would then be to improve diagnosis. To achieve this it is first important to consider the probability of a PAD diagnosis. Secondly, atypical symptoms should be interpreted with more care and leg pain evaluated correctly. Liberal use of ABI measurements is also important. In epidemiological surveys and quality assurance registers should use standardized questionnaires that including HRQL. Another key issue is women's misinterpretation of PAD and other CVD symptoms [183]. This can be corrected by patient education.

Another way to improve awareness is to review and up-date our PAD treatment and management guidelines. The SPPS cohort displayed significant differences in use of preventive drugs (Study II) among the PAD stages. This is in concordance with the current guidelines, but there is very little scientific support for this approach and rationale

behind these guidelines is not easy to follow (Table.5). Research on benefits of risk factor modification and determination of the best medical treatment for PAD patients with or without symptoms has lagged far behind. A part of this is the lack of cost-effectiveness analyses. Risk reduction would probably be equally beneficial in all PAD stages and the diverging guideline recommendations for prevention of CV risk in APAD subjects is a severe problem.

A key issue needs to be discussed is whether screening programs using ABI should be considered [202]. ABI could easily be applied in routine clinical practise but today there is lack of support among physicians and the current guidelines do by a large extent not support preventive therapy for APAD. If screening is instigated there would be treatments available. The WHO has defined screening as a medical investigation that does not arise from a patients' request for advice for specific symptoms or complaints [203].

Table 13. Applicability of WHO screening criteria on PAD.

	WHO Screening criteria	Valid for PAD
1	Important health problem	Yes (PAD afflicts 20% of elderly)
2	Accepted treatment for recognized disease	Yes
3	Facilities for diagnosis and treatment	Yes (ABI and available guidelines)
4	A latent and a symptomatic stage	Yes
5	Suitable test	Yes (ABI, easy to use, safe, cost-effective)
6	Acceptable test to population	Yes (minor discomfort)
7	Natural history of condition understood	Yes
8	Agreed policy on whom to treat	Yes (if screening will be established)
9	Cost of findings economically balanced with overall health	Yes
10	Case finding should be a continuous process	Yes (if screening will be established)

It seems possible that PAD fulfils the WHO criteria for a disease suitable for screening (Table 13), although the cost-effectiveness of the screening procedure needs to be proven.

FUTURE ASPECTS

There are many areas to target for future epidemiological research on PAD. This thesis has identified questions that need to be answered before major advances in treatment of PAD can be accomplished.

Questions such should include pain, tissue loss and need for interventions.

Another area that has raised questions is the different prevalence rates between men and women. There are obvious biological differences between men and women in distribution of atherosclerosis and disease onset time. The influence of sex hormones, such as estrogen has been the main target for research in sex differences, but in particular for peripheral manifestations of atherosclerosis scientific evidence is still lacking. Future studies should be designed as a cohort follow up study that evaluates the influence of risk factors and preventive interventions out of a gender perspective. ABI validity issues may also influence prevalence data for PAD. A study that clarifies sex differences in ABI measurements can be executed by performing several small methodological studies focusing on ABI levels in healthy men and women.

Improvement is also needed in understanding the impact of PAD on functional capacity in older persons. PAD is suggested to accelerate the speed of functional decline [204] Our studies indicate that men and women present IC symptoms differently and women may be underdiagnosed. Interesting future research should focus on development of diagnostic tools for IC. A better

understanding of the spectrum of clinical pictures presented can be highlighted by development of new questionnaires and interviews questions covering IC symptoms.

CVD prevention with drugs is an area that largely is undeveloped in PAD. Future studies should be performed in PAD subjects only and enrol enough patients to enable evaluation of sex differences and the different PAD stages. The first studies should probably evaluate single treatment with target drugs to be followed by multiple drug strategies.

Finally it is an urgent task to review and update the current guidelines in concordance with available data on risk reduction and cost benefits of treating PAD subjects with preventive drugs. Despite beneficial pleitropic effects of both statins and ACE-i, regardless off lipid- or blood pressure treatment goals, are these drugs not recommended for all PAD subjects. Evidence is conflicting especially for the widely recommended drug aspirin.

SUMMARY AND CONCLUSION

I. PAD is common in older age groups and most subjects with the disease are asymptomatic. Women dominate among those with PAD when definition is based on ABI and the prevalence differs between Swedish regions. SLI as a measure of CLI seems to be present in 1% of the population over 60 years.

II. Almost half of the PAD subjects did not have known CVD, and co-morbidity was associated with a more advanced stage of PAD. Forty percent of PAD subjects reported a life-long no smoking history. Smoking appeared as a risk factor already after ten years of smoking for women as compared with 30 years for men. Only a minority of subjects reported use of preventive drug, and men used it more frequently as compared to women.

III. When determining IC prevalence using Rose questionnaire and ABI, it tends to be more common among men. Men and women with diagnosed IC appear to have the same disease and mobility when objective measures of atherosclerosis is leg arteries such as ABI, DUS and walking distance are employed. Women with IC report atypical symptoms more frequently than men

IV. Medical treatment for preventing CV events in APAD subjects seems to be cost-effective and among the evaluated treatment strategies, ACE-i displayed the largest reduction in event rates to the highest mean QALY. Aspirin treatment does not appear to be cost-effective due to low reduction in event rates.

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