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Cardiovascular Risk Assessments in Peripheral Arterial Disease - results of a ten-year follow-up of a Swedish population-based cohort

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CARDIOVASCULAR RISK ASSESSMENTS IN PERIPHERAL ARTERIAL DISEASE - RESULTS OF A TEN-YEAR FOLLOW-UP OF A SWEDISH POPULATION-BASED COHORT

THESIS FOR DOCTORAL DEGREE (Ph.D.)

by

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"I have learned you are never too small to make a difference."

Greta Thunberg

POPULAR SCIENCE SUMMARY

Peripheral Arterial Disease (PAD) is an atherosclerotic condition that is common in the elderly population and is associated with high risks for adverse Cardiovascular (CV) events and an increased mortality. Since this condition has an easily detected subclinical phase, screening and early CV prophylactic treatment may be beneficial. This remains however to be confirmed in scientific studies. PAD is diagnosed by an index of the systolic blood pressure in the ankle and the arm; the ankle brachial index (ABI). The cut off value for diagnosis is commonly set to <0.9. The guideline recommended calculation method is to divide the highest blood pressure in each leg by the highest systolic blood pressure in the arm [1]. There is today, however no consensus on which ankle blood pressure to use for ABI calculation in public health activities.

The general rationale for this project was the need of improved and updated knowledge about the natural history for PAD and its associated CV risk. Most studies of PAD prognosis and outcome have become outdated [2, 3]. Further have few studies addressed population-based cohorts and asymptomatic PAD subjects (APAD) [4, 5]. Accordingly, the overall aim of this project was to determine the current national history and risk for CV events for different PAD stages. The project was based on a ten-year follow-up of a population-based cohort captured in 2005. Data was collected by ABI measurements, questionnaires, and national registry data.

The ten years mortality was found to be doubled among PAD subjects as compared the references (60 % versus 27%), which was comparable with results presented for almost two decades ago. This contrasts to Coronary Artery Disease (CAD) and Cerebrovascular Disease (CVD) where large improvements in survival are observed. Death was attributable to a CV event in 38% for PAD and 12% among references. Some 60% of symptomatic PAD subjects were offered CV preventive medication. The APAD subjects, who are the main focus for preventive healthcare possibilities were further analysed. They consisted of a heterogenic population, with different levels of risk, dependent on comorbidity. Overall, the mortality rates were similar with the symptomatic group. Comorbidities, as previous CAD or CVD, conferred increased risk, as did concomitant hypertension, diabetes mellitus and smoking, particularly among women. The presence of APAD, almost doubled the CV risk. Thus, may ABI measurements be of interest for improved risk reduction strategies.

Two different ABI calculation methods were used for assessment of PAD prevalence and CV risk. When using the lowest ankle blood pressure for the ABI calculation, the prevalence was 16% and 10% when using the highest. CV risk was significantly increased for subjects with

ABI<0.9 regardless of method. Finally, the predictive value of an ABI<0.9 for a future CV event was assessed and was found to be low for both methods.

In summary, this project covers some fundamental background data on natural history for all PAD stages and consequences of different ABI calculation methods. This data is necessary for consideration of screening and subsequent improved treatment with the ultimate goal to prevent atherosclerosis development.

POPULÄRVETENSKAPLIG SAMMANFATTNING (SWEDISH SUMMARY)

Benartärsjukdom är en manifestation av den systemiska sjukdomen åderförkalkning som också kallas arterioskleros. Den utgörs av förträngningar som uppstår i benens pulsådror och kan ge symtom i form av smärta i benen vid ansträngning eller i värsta fall även i vila eller med sår på fötter och underben. För de allra flesta är dock tillståndet symtomfritt, men kan ändå diagnosticeras med enkla metoder. Individer med benartärsjukdom har oavsett symtom en förhöjd risk att drabbas av andra tillstånd som beror på åderförkalkning, exempelvis hjärtinfarkt eller stroke.

Benartärsjukdom är ovanlig hos unga men vanlig hos äldre och förekommer i upp till 20% av befolkningen över 60 år och ökar med åldern. Utöver stigande ålder och ärftliga betingelser finns det medicinska tillstånd som ökar risken för benartärsjukdom, till exempel högt blodtryck, hög blodfettsnivå eller diabetes. Därtill finns det andra orsaker som är beroende av livsstil såsom rökning, övervikt och bristande fysisk aktivitet.

Diagnosen för benartärsjukdom ställs enkelt genom en beräkning av kvoten mellan blodtrycket i ankelnivå och arm. Internationella riktlinjer rekommenderar att det högsta uppmätta blodtrycksvärdet i arm och ankelnivå används, men kunskapen om optimal metod är osäker.

Behandling av benartärsjukdom rekommenderas av två viktiga skäl, dels för att minska risken för att drabbas av hjärtinfarkt eller stroke och dels för att minska risken för försämrad blodcirkulation i benen med svårare bensymtom som följd. Behandlingen är inriktad på livsstilsberoende faktorer och läkemedelsbehandling. med syfte att skydda blodkärlen och bromsa åderförkalkningen. Vid mycket svåra symtom av nedsatt cirkulation i benen kan kärlkirurgisk behandling bli aktuell för att lindra symtomen. I vissa fall kan åderförkalkningen vara så utbredd att kärloperationer inte hjälper. I dessa fall kan amputation vara det bästa behandlingsalternativet.

Hjärtinfarkt, stroke eller benartärsjukdom med symtom är alla tillstånd där livskvaliteten påtagligt kan försämras och behandling av dessa genererar höga kostnader för samhället. För framtiden beräknas dessa kostnader öka i takt med att befolkningen lever längre och fler förväntas bli drabbade. Genom en förbättrad förebyggande behandling, eller en behandling i tidigt skede, kan sjukdomens konsekvenser i form av lidande och kostnader minskas.

I detta forskningsprojekt har vi införskaffat grundkunskaper om naturalförlopp av benartärsjukdom och hur väl vi i Sverige efterlever behandlingsrekommendationer i förhållande till internationella riktlinjer. Sådan kunskap har till viss del saknats och är nödvändig att besitta vid övervägande av införande av långsiktig förebyggande behandling. Vidare har effekten av olika beräkningsmodeller för ankel-arm kvoten studerats avseende möjlighet att identifiera individer med framtida risk för att drabbas av en hjärt-kärlhändelse.

Denna avhandling består av fyra delarbeten som baseras på långtidsuppföljning av en grupp om 5080 individer i åldrarna 60 - 90 år. Dessa valdes slumpmässigt ut från fyra olika svenska samhällen och undersöktes med enkäter avseende hälsa, läkemedelsbehandling, förekomst av rökning, bensymtom och gångförmåga samt mätningar av blodtryck i arm och ankelnivå. Individernas hälsotillstånd har följts genom analys av från sjukvården inrapporterade uppgifter till Socialstyrelsen mellan åren 2005 - 2015.

Delarbete I beskriver dödligheten och dödsorsaker för individer med benartärsjukdom av olika svårighetsgrad. För individer med benartärsjukdom var dödligheten 60% jämfört med 27% för individer utan benartärsjukdom. Dödsorsaker berodde i 45% av fallen på hjärt-kärlsjukdom (huvudsakligen hjärtinfarkt och stroke) för individer med benartärsjukdom jämfört med 31% för referenserna. Ju svårare benartärsjukdomen var, desto högre var risken för död. Till skillnad mot hjärtinfarkt och stroke, där överlevanden påtagligt har förbättrats över tid, är dödligheten för de med benartärsjukdom oförändrad jämfört med för 20 år sen.

Delarbete II beskriver sjukligheten och läkemedelsbehandling för individer med benartärsjukdom. Individer med benartärsjukdom drabbades nästan dubbelt så mycket av andra sjukdomar såsom hjärtinfarkt, stroke, diabetes och njursvikt jämfört med individer utan benartärsjukdom. Dödligheten var högre bland män med benartärsjukdom än kvinnor. Cirka 60% av individerna med symtomatisk benartärsjukdom erhöll läkemedelsbehandling i enlighet med internationella riktlinjer år 2015. Det finns sannolikt flera förklaringar till denna underbehandling. Kunskapsläget om sjukdomens elakartade förlopp kan vara en förklaring. Andra förklaringar kan vara bristen på studier av denna population liksom otydligheten kring vem som ska behandla dessa patienter, viket behöver inventeras vidare.

Delarbete III fokuserar på individer med symtomfri benartärsjukdom. Symtomfri benartärsjukdom medförde en nära fördubblad risk för död i hjärt-kärlsjukdom. Högst risk sågs hos individer med symtomfri benartärsjuk och hjärtsjukdom eller stroke. Störst inverkan på risk, beroende av benartärsjukdom, sågs hos individer med högt blodtryck, diabetes eller rökning. Dessa grupper saknar oftast skyddande läkemedelsbehandling och skulle kunna vara intressanta för fortsatta studier av screening och behandling för benartärsjukdom.

Delarbete IV jämför två sätt att beräkna ankel-arm kvot för diagnostik av benartärsjukdom med avseende på förekomst samt risk för framtida ohälsotillstånd av hjärt-kärlsjukdom. När det lägsta ankel blodtrycksvärdet användes hittades 70% fler individer med förhöjd risk.

Slutsatser: Vi har visat att individer med benartärsjukdom har en nästan dubblerad risk att drabbas av hjärtinfarkt eller stroke trots att de är symtomfria. Individer med symtomatisk benartärsjukdom är ofta bristfälligt behandlade med läkemedel. Vi föreslår att man fortsättningsvis riktar studier av screening för benartärsjukdom emot patientgrupper över 60 års ålder, som redan har förhöjd risk för hjärt-kärlsjukdom men är utan behandling mot sådan, således till exempel individer med högt blodtryck, diabetes eller rökare.

ABSTRACT

Background An updated knowledge on natural history in Peripheral Arterial Disease (PAD) is lacking, in particular for the asymptomatic stage (APAD). The disease has strong associations with other atherosclerotic manifestations such as myocardial infarction or stroke, which could be prevented with prophylactic measures. PAD is easily detected through simple ankle and brachial blood pressure measurements, why screening for this condition has been suggested but is yet not proven cost-effective. Identification of PAD could be useful in cardiovascular (CV) risk assessments. To improve health in society and to reduce costs for care, improved prophylactic strategies is needed in CV management. Before that, improved knowledge of the natural history of PAD is essential. This project describes mortality, CV outcome and treatment patterns in symptomatic and asymptomatic PAD men and women.

Methods and Results

Study I A population sample of 5080 subjects, selected through randomization, was enrolled in the study in 2004-2005. Participants completed health state questionnaires and underwent ankle brachial index (ABI) measurements for classification into PAD severity stages. A follow-up was conducted by the end of 2015 using data from Swedish governmental national registers for cause of death, which was compared with the PAD stage determined at baseline in 2005. The age-adjusted hazard ratios for a main cause of death by a CV event were 1.9 [95% CI 1.5-2.3] in Asymptomatic PAD, 2.6 [95% CI 2.1-3.4] in Intermittent Claudication, and 3.5 [95% CI 2.3-5.2] in Severe Limb Ischemia stage groups.

Study II This was a prospective observational population-based cohort study based on physical examinations and questionnaires at baseline supplemented with national register data between 2005 and 2015. Subjects were placed in subgroups defined by ABI levels and reported symptoms as in study I. After adjustments for age, comorbidity, and sex, the risk was almost doubled for CV death in Intermittent Claudication and APAD subjects (HR 1.95 and 1.80) as compared to a reference population. The risk for other comorbidity as diabetes, non-fatal myocardial infarction and stoke and renal failure was doubled in PAD. Some 60% of symptomatic PAD subjects received the pharmacological prophylactic treatment as recommended in guidelines.

Study III This study evaluated the risks for adverse CV events in subjects with APAD in combination with different known traditional CV risk factors over a ten-year observation period. For subjects with hypertension at baseline the CV mortality incidence was 35.4 deaths per 1000 person-years when combined with APAD and 11.7 without. In women with hypertension but without other risk factors, presence of APAD increased the age-adjusted Hazard Ratio (HR) for fatal and non-fatal CV events by 1.86 [CI 1.54,2.24, p<0.001].

Study IV This prospective study assessed the differences in CV outcome if using the highest (ABI-HI) or lowest (ABI-LO) ankle blood pressure for ABI calculation for PAD diagnosis in a population-based cohort. The prevalence of PAD, defined by an ABI<0.9, by using ABI-LO

and ABI-HI was 16.3% (n=799) and 9.6 % (n=469), respectively. For the subgroups defined by ABI-LO and ABI-HI, the age-adjusted HR [95% CI] for the composite outcome CV mortality and non-fatal CV events, was 1.25 [1.06-1.49] and 2.11 [1.85-2.39] respectively. The predictive value of an ABI<0.9 to foresee a future event was low for both calculation methods.

Conclusions The mortality is more than doubled in symptomatic PAD patients compared with reference subjects and increase by severity of PAD stage. The prognosis for this group has not changed over the last decades in contrary to other CV manifestations. Among all PAD subjects, CV causes were the most common main cause of death (45%) and a CV event was present as either the main or one of the three most common contributing causes of death in 64% of the cases. APAD subjects confer almost similar risk for CV events as symptomatic patients. PAD is more common in women, but men face a higher risk for death and CV events. Some 60% of symptomatic PAD subjects received prophylactic drugs according to guidelines by 2015. Subjects with APAD and any other CV risk factor have significantly higher risks for CV events and could therefore constitute suitable populations for further studies of screening with ABI measurements and subsequent intensified CV prophylactic treatment. When using the ABI-LO method more subjects at risk were identified, but their average risk was lower when comparing to the ABI-HI method which identified less subjects at risk. These differences are important to be aware of in further studies of screening. ABI measurements should be considered an important indication in aggressive multifactorial risk factor reduction in populations with any other prevalent CV risk factor.

LIST OF SCIENTIFIC PAPERS

I.   **Sartipy F**, Sigvant B, Lundin F, Wahlberg E Ten Year Mortality in Different Peripheral Arterial Disease Stages: A Population Based Observational Study on Outcome *European journal of vascular and endovascular surgery: the official journal of the European Society for Vascular Surgery 2018;55(4):529-536*

II.   **Sartipy F**, Lundin F, Wahlberg E, Sigvant B Cardiovascular long-term outcome and prophylactic treatment patterns in peripheral arterial disease in a population-based cohort *European heart journal. Quality of care & clinical outcomes 2019;5(4):310-320*

III. **Sartipy F**, Fihlo A J G P, Lundin F, Wahlberg E, Sigvant B Presence of Asymptomatic Peripheral Arterial Disease in Combination with Common Risk Factors Elevates the Cardiovascular Risk Substantially, *Submitted*

IV.   Fihlo A J G P, **Sartipy F**, Lundin F, Wahlberg E, Sigvant B Assessments of different modes of ankle-brachial index calculation for prediction of cardiovascular risk, *Submitted*

CONTENTS

LIST OF ABBREVIATIONS

ABI	Ankle-Brachial-Index
APAD	Asymptomatic Peripheral Arterial Disease
CAD	Coronary Artery Disease
CDR	Cause of Death Register
CLI	Critical Limb Ischemia
CV	Cardiovascular
CVD	Cerebrovascular Disease
FRS	Framingham Risk Score
HR	Hazard Ratio
IC	Intermittent Claudication
LEAD	Lower Extremity Artery Disease
LRF	Lifestyle Risk Factor
NPR	National Patient Register
PAD	Peripheral Arterial Disease
PCSK-9	Proprotein Convertase Subtilisin/Kexin type 9
PDR	Prescribed Drug Register
REF	References
SGLT-2	Sodium Glucose CoTransporter 2
SLI	Severe Limb Ischemia
Swedvasc	Vascular Registry in Sweden

INTRODUCTION

Peripheral Arterial Disease (PAD) is a manifestation of the systemic disease atherosclerosis. It is caused by thickening of the arterial walls that narrows the vessel lumen. PAD can occur in all peripheral arteries, but mainly concerns vessels in the lower limbs. The vessel narrowing cause a reduction in blood flow that results in pain when there is an increased demand during exercise. In severe cases blood flow to the distal parts of the leg is insufficient and pain at rest or ischemic ulcers appear. This is associated with a major risk for amputation and disability. For many patients the PAD is asymptomatic but the mild arterial constriction can still be detected at rest through simple measurements of blood pressure at the ankle level and in the arm. Regardless of symptoms, presence of PAD is a manifestation of atherosclerotic disease and is associated with an increased risk for cardiovascular (CV) events such as myocardial infarction and stroke.

PAD generally develops slowly and is rare among young but is common among elderly where almost 20% of the population over 60 years is affected. The occurrence of PAD in populations increase with age and several risk factors make it more likely to occur. Examples of such are other medical conditions, i.e. hypertension, diabetes mellitus or hyperlipidemia. Life-style dependent activities such as smoking and low physical activity also increases this risk.

Interventions are indicated to reduce the risk of CV events and to alleviate limb symptoms. Treatment is designed to act versus risk factors that promotes atherosclerotic evolution and thereby to protect the vessels and to improve physical ability. An initial advice to PAD patients is often to modify an unhealthy lifestyle, meaning encouragement of smoking cessation, weight reduction and exercise. Secondly, pharmacological treatment is indicated to treat the mentioned common comorbidities hypertension, hyperlipidemia and diabetes. For the late stages with severe limb symptoms, vascular interventions may be indicated. Such procedures often reduce ischemic symptoms and improves ambulation but sometimes the atherosclerosis is so generalized that vascular interventions are futile and an amputation is needed.

Myocardial infarction, stroke or PAD are all conditions that can have major impact on quality of life for the patient and is also costly for society. The resources needed for these atherosclerotic manifestations are expected to increase because of the growing elderly population despite successful new treatment strategies. For PAD in particular, more widespread recognition and implementation of intervention strategies could maintain health and the quality of life of the patients. It could also reduce costs for society.

In this thesis, the long-term consequences of PAD are evaluated, and to what extent international treatment guidelines are implemented in Sweden. Knowledge of the natural history of PAD and the factors influencing it is essential when considering improved prophylactic drug interventions.

GENERAL BACKGROUND AND LITERATURE REVIEW

ATHEROSCLEROSIS

Atherosclerosis

The terms atherosclerosis and arteriosclerosis are often used interchangeably in the literature, but there is a difference. Arteriosclerosis refers to a general hardening of the arterial walls making them stiff and thick instead of flexible and elastic, while atherosclerosis refers to arterial hardening of the vessel wall due to the build-up of atherosclerotic plaques that consists of fats and other substances. Originally, atherosclerosis derives from the Greek words *athero* – meaning gruel and *sclerosis* meaning hardness.

Atherosclerosis is not only a "modern" disease caused by contemporary lifestyles but is reported from several preindustrial and even preagricultural populations [6]. One of the first reports about hardening of the arteries were written in the 16th century [7]. Considerable advances in scientific understanding of atherogenesis were made in the 1960th, when three main events for plaque formation were outlined; intimal proliferation of smooth muscle cells, formation of tissue matrix and the deposition intra-and extracellular lipids [8, 9].

Atherogenesis

The normal arterial wall consists of three layers, the intima, media and adventitia. The intima is the inner lining and consists of a single layer of endothelial cells. Atherogenesis is initiated with the formation of plaques through the intima layer. This complex process still is not fully understood but can be divided into five key steps: 1) endothelial dysfunction, 2) formation of lipid layer or fatty streak within the intima, 3) migration of leukocytes and smooth muscle cells into the vessel wall, 4) foam cell formation and 5) degradation of extracellular matrix [10]. Endothelial dysfunction, the primary event, is multifactorial but involves shear stress from nonlaminar blood flow and impact of biological and chemical irritants causing oxidative stress and inflammatory reactions. The disruption of the endothelial barrier allows passage of lipoproteins into the intima where it accumulates. This is accompanied by an inflammatory process in the vessel wall that includes recruitment of white blood cells from the blood. These

cells enter the arterial wall and consumes lipoproteins and develops into foam cells. This causes a compensatory remodeling process to occur in the subintimal layer and lets smooth muscle cells migrate from the media to the intima causing the plaques to expand further. Eventually this reduces arterial lumen and may obstruct blood flow due to increased resistance. One such plaque may rupture into the vessel lumen, causing thrombosis. The mechanism following this rupture are activation of platelets and a consequent thrombus formation and may cause a local arterial occlusion. Another feared consequence is embolization. Thrombus formation and embolism can occur without symptoms or with major clinical complications as in stroke, for instance.

Atherosclerosis has also emerged as a chronic inflammatory disease with an autoimmune component. Multiple pathways for plaque evolution with time is possible, including continuous endothelial damage and inflammatory activity. This evolution is driven by risk factors such as hyperlipidemia [11], diabetes [12], hypertension [13], smoking [14] and other conditions that causes oxidative stress in the arterial wall [15].

Clinical manifestations

Atherosclerosis is initially asymptomatic and symptoms appear first when arterial lesions impede the blood flow. Plaques occur mostly in focal areas of the arterial vasculature where blood flow tends to be turbulent [16]. Common distribution of occlusive atherosclerotic disease are the coronary and the carotid arteries, the visceral branches of the abdominal aorta and the terminal parts of abdominal aorta including the arteries to and in the lower limbs [17]. Hence, typical symptoms depend on the site of the lesions in artery to the organ they supply and could be divided into domains. Often symptoms are transient, as in exertional angina pectoris and intermittent claudication, and caused by the inability of the arteries to dilate and adapt to an increased blood flow demand. This is a result of a combination of stiff vessel walls and atherosclerotic plaques. Ischemic symptoms may also present suddenly but is not transient and cause end organ ischemic consequences. Examples are stroke and heart infarction, where plaque rupture initiates a local thrombus formation or embolism often is contributing or the main mechanism.

Common characteristic atherosclerotic symptoms, separated by arterial domain, are briefly:

- Coronary area: The typical presentation is chest pain, most often localized under sternum or the left side of the chest. The pain sometimes spreads to the jaw, left shoulder or the arm. When symptoms is present also at rest, the condition is unstable and should

be considered a medical emergency. Similar symptoms is a result of myocardial infartion, often accompanied by tightness in the chest, sweating, anxiety and shortnesss of breath. Chronic cardiac failure is often caused by chronic ishemic heart disease and may present with a variety of different symtoms [18].

- Cerebrovascular area: Atherosclerotic manifestations in this area are transcient ischemic attack (TIA), and minor and major stroke due to ischemic or hemorrhagic events. Different events present with different symptoms, common are paralysis, confusion, unilateral loss of vision, loss of balance, unilateral weakness, difficulties in communication including speech disturbances, unconsciousnesss and headache. In TIA, the symptoms dissapear within 24 hours. Minor stroke is defined variably in the litteature [19], but implies a less severe state than a major stroke.

- Visceral artery area: Visceral artery atherosclerosis results in manifestions depending on the organ that is affected, and blood flow obstruction causes intestinal ischemia or end organ functional disturbance of failure of the liver, spleen and kidneys. Chronic visceral artery ischemia presents as abdominal pain, typically after eating and a subsequent weight loss, and sudden total main artery total occlusion may even cause intestinal necrosis.

- Lower limb area: This area is the main focus of this thesis and is further described below.

In epidemiological studies evaluating the natural history of an atherosclerotic disease such as PAD, understanding these manifestations are essential because they are the main outcome parameters included in the CV events during follow. Diagnostic uncertainties of these events in the national registries may also influence the validity of the results in a thesis project of this kind.

PERIPHERAL ARTERIAL DISEASE

Nomenclature

The Peripheral Arterial Disease is also known as Peripheral Artery Disease and abbreviated to PAD. The term peripheral refers to "away" from the heart and brain, considered to be the central parts of the body from a cardiology perspective. PAD often also refers to the disease affecting the lower extremities. Nowadays, PAD distal to the aortic bifurcation is called Lower Extremity Artery Disease (LEAD) [20], but the terms PAD and LEAD are often used interchangeably. More appropriate may be to use PAD for disease in all peripheral arteries. A less frequently used term is Peripheral Arterial Occlusive Disease (PAOD), adding the occlusive nature of this disease.

In this thesis PAD was chosen and defined as "atherosclerotic disease affecting the lower extremities". While not entirely consistent in the literature this nomenclature is still the most common.

Pathophysiology

Healthy arteries are dynamic structures that have the ability to adapt in size to a shifting demand of blood from the end organ. The middle layer of the arterial wall consists of smooth muscle cells that can contract and reduce the lumen of the artery when blood requirements distally is low, such as at rest for the legs. It also has the ability to dilate and allow more blood flow when needed. This mechanism behind this adaptation is a complex interplay between shear stress, as well as regulation and expression of vasoactive peptides and proteins in the intima and media [21].

In atherosclerosis the arterial wall becomes stiff and more inert and loses its adaptive ability to changes in blood flow requirements. In APAD, no arteries have enough obstructing atherosclerosis to cause symptoms but plaques are still extensive enough to cause a blood pressure drop between the arm and the ankle level at rest. When blood flow is obstructed more drastically end organ ischemia occurs during daily activities. In the leg this end organ is skeletal muscle that have very low blood flow demand at rest, which increases up to 40 times during exercise. Early in the course of disease blood flow compensation is possible by evolution of preexisting collateral arterioles to larger conductance vessels. This process is called arteriogenesis [22] and is driven by increases of shear stress in these arterioles. There is a heterogeneity in the arteriogenic ability among patients with PAD [23]. Simultaneously, the

intermittent ischemia that occurs in skeletal muscle in IC [24] alters the cellular metabolism which induces the pain and leads to disturbed cellular and mitochondrial activity [25]. Recent advances in understanding PAD pathophysiology have identified mitochondrial processes as a key element in causing PAD symptoms [26].

Clinical presentation

The most common presentation of PAD is a painful ache in one or both of the legs that appears when walking and disappears at rest. This is named Intermittent Claudication (IC). Symptoms generally develop slowly over time but could suddenly get worse and might in such situation demand for immediate vascular surgery. Often, however, they are less pronounced and vague [27], especially among women, and be described by the patients as numbness in the legs when exercising. In more severe disease symptoms at presentation may include loss of hair on legs and feet, numbness, slow growing toenails, pale skin color, leg muscle atrophy, foot ulcers and pain at rest, defined as Critical Limb Ischemia (CLI). This state is often a constant agonizing condition with severely reduced quality of life. CLI is the most common cause of non-traumatic lower limb amputations in the US [28], but less prevalent than the other stages. The most prevalent stage in the general populations is APAD [29].

Although most PAD subjects are asymptomatic, they nevertheless have extensive atherosclerotic lesions. About one third of APAD subjects have limited walking ability due to other diseases and therefore do not experience typical leg symptoms [30]. Consequently, they could in fact have a "masked" IC. The incoherence between leg symptoms and atherosclerotic burden as well as presence of other comorbidities makes studies of PAD natural history challenging. It also may explain why some APAD subjects rapidly deteriorates into CLI.

Atherosclerosis causes >90% of the PAD cases [31] and atherosclerotic PAD is the focus of this thesis. There are, however other causes that often occur at younger age [32]. Examples are popliteal artery entrapment syndrome [33] and cystic adventitial disease of the lower extremity arteries [34].

Disease classification

In vascular surgery, stages of PAD are classified in order of severity either according to the Fontaine [35] or Rutherford classifications [36]. The main purpose with these classifications is to

make comparisons possible when different institutions describe their patients and treatment outcomes. While Fontaine is based exclusively on clinical symptoms ranging from asymptomatic to ischemic gangrene, Rutherford's classification adds clinical symptoms to findings from the patient's examination and basic limb blood flow assessments. As mentioned previously is the first PAD stage asymptomatic according to Fontaine, and the next stage IC is defined by patients' report of the symptoms described above. CLI is diagnosed when reported symptoms are severe and rather constant as described [37]. Rutherford's classification resembles Fontaine's but adds physical assessments with treadmill test and ABI measurements, for example, that helps to differ from pseudo-claudication [38].

A more recent classification with the same purpose is published in the Trans-Atlantic Inter-Society Consensus Document (TASC) guidelines [39]. It was updated as TASC-II [40] in 2006. This document adds anatomical description of the atherosclerotic lesions found in the PAD patient. Lately, two classification systems targeting CLI stage is established; the WIfI (Wound, Ischemia, and foot Infection) scale [41], and the Angiosome concept [42]. A high WIfI stage strongly increase the likelihood of having an amputation in CLI, why this classification scale has become useful in the preoperative evaluation before vascular interventions [43].

For risk assessment, and determination of PAD natural history such as in this thesis it is important to use a clearly defined PAD classification. Ideally it should be possible for any reader to interpret the findings and apply them to their own experiences. Unfortunately, it is difficult to use classification initially designed for vascular interventions for epidemiological studies of this kind. For instance, in this thesis a slightly different definition of CLI had to be used.

Diagnostics and investigations

In general, the PAD diagnosis is confirmed in primary care clinics, where the physician asses the typical symptoms in the medical history and findings in the physical examination. The latter includes palpation of leg pulses and measurements of systolic blood pressures at the ankle level and in the arm using a cuff and a doppler probe. The quota of these pressure measurements is the ankle-brachial index (ABI), which for healthy persons is between 0.9 -1.4. Any value below 0.9 is considered pathologic and is enough to make the diagnosis PAD. Over the cut off value of 1.4, the lower limb arteries are considered less compressible and stiff as a consequence of PAD [44].

The ABI test is easily performed and has a sensitivity of 69-95% and specificity between 56-99% for detection of PAD using angiography as gold standard [45]. The ABI test has been

performed using different practises, which may impact on the variations in sensitivity and specificity seen. The guideline recommended way of calculating the ABI is to use the highest blood pressure obtained at the ankle level. This method has been employed mainly before and after vascular surgery. An alternative method to calculate ABI is more suitable for CV risk assessments in public health. It utilizes the lowest blood pressure measured at the ankle level for the ABI calculation [46]. Such differences in methodology affects the identification of PAD and its different stages that all relies on the ABI test. When the diagnosis is difficult, further investigations may be necessary. Examples of such are measurements of toe blood pressures, transcutaneous oxygen pressure and treadmill tests. In this thesis no other diagnostic test than ABI is used.

When symptoms are severe enough, surgery may be required, as well as a preoperative work up. One example is duplex ultrasound for rapid localization of arterial stenoses and assessment of blood flow. Before interventions advanced imaging techniques such as computed tomography angiography and contrast-enhanced magnetic resonance imaging may also be warranted.

Epidemiology

PAD is a global non-communicable vascular disease that mainly affects the population over 60 years of age. In 2018, it was estimated that over 200 million people have PAD worldwide [31]. Its prevalence varies between 5 to 25% [47, 48], depending on study population and methods used for diagnosis. In many epidemiologic studies, presence of PAD in a subject is defined as having an ABI<0.9 with or without symptoms [49] or having undergone a peripheral vascular intervention.

In the US, in the year 2000 the prevalence of PAD was 4.3% in populations over 40 years old, and 14.5% among those over 70, affecting a total number of 8,5 million people [50, 51]. The Swedish point prevalence study covering subjects 60-90 years old reported that 18% had any type of PAD, while as 6.8% had IC and 1.2% severe limb ischemia (SLI), which was used as proxy for CLI [52]. This Swedish prevalence study gathered the cohort on which this thesis is based upon. During the last decade, the numbers of individuals affected by PAD increased by 28.7% in low- to middle-income countries and 13.1% in high-income countries [47].

As mentioned previously, does PAD belong to the CV disease area, which according to the WHO causes 31% of all deaths worldwide. The mortality is mainly caused by myocardial infarction (85%) or a stroke [53]. There are reports of declining mortality rates for CV during the last two decades [54-56]. In the UK, for instance, a corresponding pattern is noted with a declining

CV mortality but a stable mortality rate for PAD [57]. Similar trend is observed in Sweden according to data from the National Board of Health and Welfare from 2017. It is proposed that less frequent smoking habits and treatment of hypertension, diabetes and dyslipidemia has contributed to the declining CV mortality, but remains unclear why PAD not shows similar improvement trends [58]. One speculation is that information about the current natural history of PAD is missing and when available variable [59]. This thesis aims to contribute to this knowledge gap and further use this information to explore if subjects with the easily detected subclinical phase APAD could be eligible for preventive measures.

Few studies on PAD focus on sex differences. The burden of CV disease is heavier in men than women until after menopause, after which the prevalence of CV disease in women exceeds that of men [60]. PAD tends to be more common among females [52, 61], an observation that partly is a result of higher CV mortality at earlier ages in men. Cellular mechanisms of gender differences is unknown but the scientific support for gender-based differences is growing [62]. One possibility is that the female hormone estrogen has protective effects in PAD development. Postmenopausal hormone therapy has therefore been suggested to reduce atherosclerotic evolution but not yet demonstrated to protect persons from PAD [63].

In women, PAD cause more pain on exertion and a greater walking impairments than in men [64], but women also tend to be older and more fragile at the time for diagnosis. Among women with abnormal ABI, 95% do not report symptoms [63], why screening for PAD in women with concomitant CV risk factors may be appropriate. Future studies on atherosclerotic disease need to focus more on differences between the sexes.

Peripheral arterial disease and comorbidities

PAD subjects are more affected by other comorbidities such asischemic heart disease, stroke/TIA, diabetes mellitus, hypertension and renal failure than people without PAD [65]. All these conditions contribute to the increased morbidity and mortality rate seen in the PAD group. Concomitant diabetes mellitus is associated with elevated risk for lower limb amputation [66] and mortality [67] in subjects with PAD. Particularly poor outcome is reported for PAD cohorts combined chronic kidney disease [68].
The metabolic syndrome have repeatedly been proven associated with PAD [69, 70].
PAD is also strongly associated with other diseases dependent on smoking habits. For example, 3.25% of a group of patients undergoing to peripheral vascular surgery had lung

cancer [71]. In Chronic Obstructive Pulmonary Disease (COPD), the prevalence of PAD is almost doubbled [72]. In patients with psychiatric disorders such as schizophrenia and dementia PAD is more common than in the general population [73, 74].

Peripheral arterial disease and lifestyle

In addition to the heavy prevalence of comorbidities associated with PAD, subjects are also more affected by lifestyle risk factors (LRF) than a reference population. As for other CV diseases, smoking, low physical activity and obesity are the most common [75]. To which extent these risk factors occur in PAD is not determined in detail, nor the increased CV risk their presence may cause in PAD. For CV disease in general, addressing LRF has gained more attention globally for reducing CV morbidity and mortality [76, 77]. Its potential is high considering of its low costs with a minimum of negative side effects, but patients' compliance with programs is often an issue [78], [79]. Better knowledge of LRF incidence in PAD is likely to be essential for developing prophylactic strategies.

Natural history

Between 30-50% of PAD cohorts have CAD manifestations [47, 80] and 15-25% carotid stenosis [81]. Most studies of the natural history of the PAD patient include risk estimates for fatal and non-fatal CV events and rarely report disease development in the affected limb. Examples of such studies are listed in Table 1 below. Presented mortality rates vary in the literature with hazard ratio (HR) between 1.1 to 6.6. The large variation is caused by differences in cohort compositions and study designs and makes comparisons difficult. For example, few designed reports on gender differences [82-85], and the method used for ABI measurements is inconsistent and often not reported.

This thesis does not address the natural history of limb symptoms in PAD, but over a mean observation time of 6.3 years, 21% of IC subjects developed CLI and 4-27% were amputated in a recent meta-analysis [86]. Previously, the milder stages of PAD was considered to rarely progress [87]. Multiple vascular lesions in the legs is associated with a worse prognosis [88].

Table 1. List of key publications on natural history of Peripheral Arterial Disease.

Author	Year	Study model	Study population (n)	Observation time (years)	CV-mortality hazard ratio (HR) or risk ratio (RR)
Hooi [82]	2004	Observational cohort	3649	7.2	HR 1.5
Criqui [2]	1992	Observational cohort	565	10	RR 6.6
Leng [3]	1996	Observational cohort	1592	5	RR 1.7-2.7
Newman [83]	1997	Observational cohort	1537	4	RR 3.0
Heald [5]	2006	Systematic review	44590	--	RR 1.96
Jelnes [84]	1986	Observational cohort	257	6.5	RR 2
Alberts [89]	2009	Observational cohort	67888	3	-
Caro [65]	2005	Observational cohort	16440	10	-
Lassila [85]	1986	Observational cohort	312	8.75	-
Melillo [90]	2016	Case control retrospective	181	5	-
Diehm [91]	2009	Observational cohort	6880	5	HR 2.07
Kornitzer[92]	1995	Observational cohort	2023	10	OR 3.63

RISK FACTORS FOR CARDIOVASCULAR DISEASE

Common cardiovascular risk factors

The typical risk factors for developing PAD are the same as for any CV disease [93], i.e smoking, diabetes, hypertension, hypercholesterolemia, obesity, a sedentary lifestyle, increasing age and chronic kidney disease [94][95]. Having a family history of PAD also increases the risks, indicating that the genetic predisposition matters [96].

PAD risk factor characteristics

The relationship between smoking and CV diseases in general, including all PAD stages is well described in the literature [97-99]. Smokers with PAD face an even higher risk for a CV event than patients with CAD [100]. The mechanism behind this may be a particularly strong susceptibility to endothelial dysfunction and oxidative stress [101]. As for all CV diseases, lipoprotein metabolism disturbances and a prothrombotic disposition also contributes [102][103].

There are multiple biochemical pathways that explain the relationship between diabetes and CV events. Examples are alterations of the lipid metabolism and a state of chronic inflammation [104]. PAD subjects with diabetes are a subgroup with particularly high risk for a poor outcome [105]. Also, obesity increases CV risk through similar pathways, including insulin resistance, hyperlipidemia, hypertension and diabetes. This because of a disturbed hormonal balance and an increased systemic inflammatory activity [106]. Differences have been seen in lipid distribution in CAD and PAD [107], which may explain less effect of medical treatment in PAD. Concomitant hypertension is the most common CV risk factor present in PAD patients [108]. The mechanism is not fully elucidated but might also be related to a disturbance in endothelial function [13], hemostasis and platelet function [109]. Chronic kidney disease, not only promote PAD development when present, it also is a risk factor for CV events in PAD patients [110].

Cardiovascular risk assessments

There is a trend shifting focus from treatment of established disease to prevention today [111, 112]. Before investing in efficient prevention strategies, access to good quality risk-stratification models is essential. Accordingly, has WHO proposed and validated a CV risk prediction model to estimate CV risk score in different demographic areas [113]. The model includes information on age, smoking, blood pressure, diabetes and cholesterol level, but not ABI-measurements.

PAD is indeed a manifestation of the systemic disease atherosclerosis with well-known, strong associations with CAD and CVD [2, 40, 47, 114]. As for other CV diseases would it be beneficial to identify PAD subjects with an increased risk for events that could be modified by prevention. To achieve this a reliable diagnostic tool is needed, which could possibly be applicable for ABI [115, 116].

There are reports describing models enable to predict CV risk [117, 118]. One example is the Framingham Risk Score (FRS) [119] that uses a gender-specific algorithm covering the risk factors age, smoking, hypertension and hypercholesterolemia [120]. Adding ABI to this risk-score [121] noted that the predictive accuracy was enhanced but would need validation to become useful. Its applicability is also supported in the Framingham-REGICOR study [122]. Another example is the Systematic COronary Risk Evaluation (SCORE) system from the European Guidelines on CV disease prevention [123]. SCORE estimates the 10 years risk of a fatal atherosclerotic event, in relation to age.

While not being comprehensive models for prediction, other attempts to find markers for especially high CV risk in populations are quite common. One of the most established is ultrasonic determination of wall thickness of the carotid arteries [124, 125]. PAD specific biomarkers not yet been identified, and genetic test panel data, for example the Genome Wide Association Study (GWAS), is currently under evaluation for PAD [126].

TREATMENT OF PERIPHERAL ARTERIAL DISEASE

Indications for treatment

Therapy for symptomatic PAD is indicated to reduce the overall risk of CV morbidity and reduce symptoms of the affected limb, including the risk of amputation [127, 128]. Guideline interventions aiming to modify risks are important, but preventive medication is also included for symptomatic patients. The drug classes covered are anti-platelets, lipid lowering and drugs for diabetes as well as antihypertensive treatments [129, 130]. Similar recommendations are valid for APAD except for platelet inhibition [20].

*Lifestyle intervention*s

The most important lifestyle recommendations for patients with PAD are:

- Smoking cessation

  Smoke cessation decreases the risk of adverse CV events and improves walking capacity in patients with PAD [100, 131, 132]. The protrombothic state and hemostasis abnormalities is normalzed following smoking cessation [133]. Intensive smoke cessation measures are more effective and nicotine replacement increase the success rate [134] . Relapses during the first year after quitting occurs in more than 50% of the patients [135], even more so when they continue to use electronic cigarettes [136].

- Increased physical activity

  Exercise is associated with a lower risk for developing PAD [137, 138] and supervised training is recommended in symptomatic disease [139-141]. Rehabilitation of PAD patients is availble in certain countries, but in Sweden only patients with myocardial incarction have this possibility. Recommended programs for physical activity include at least three 30-minutes exercise sessions a week for a minimum duration of three months [142, 143].

- Dietary changes

  Greater consumption of fruit and vegetables is associated with lower risk of developing PAD [144] and restricted intake of saturated fat and sodium is recommended to reduce the risk for CV events [145]. Guidelines suggests that intake of dietary fiber should be 25-30 grams daily and saturated fats less

than 7% of the total calory intake. For sodium they advise 1.5 to 2 grams per day [146, 147].

- Normalisation of body mass index

  Obesity, a Body Mass Index (BMI) >30 kg/m^2, is a risk factor for future events for all CV diseases, including PAD [148 149 150], particularly in women [151]. Normalisation of weight reduces the risk for diabetes, hypertension and the metabolic syndrome [152]. There are no specific interventions for obesity in PAD patients, and they should follow general guidelines.

A large amount of patients with high CV risks do not achieve the goals, even with the aid of pharmacological treatment [153].

Pharmacological treatment

European guidelines for PAD recommend certain pharmacological treatments for PAD patients [154].

- Lipid lowering drugs

  Lipid-lowering therapy induces plaque regression and improves endothelial function [155]. PAD patients should be treated with lipid-lowering drugs with a target serum low-density lipoprotein cholesterol (LDL-C) value of <1.8mmol/L, or a reduction of the baseline value with at least 50% (when baseline is between 1.8-3.5 mmol/L) [156]. This diminish the mortality- and amputation rates with almost 50% in CLI [157]. Guidelines recommend high-intensity statins (atorvastatin 40-80 mg or rosuvastatin 20-40 mg) in PAD patients ≤75 years of age [158]. Combination treatment with ezetimibe is advised in selected patients [159]. Lipid-lowering drugs are effective for reduction of CV events in younger, as well as in patients older than 75 years [160]. Newer drugs, such as Proprotein Convertase Subtilisin/Kexin type 9 (PCSK-9) inhibitors have been suggested for use in PAD patients [161], but their safety after long term use is not yet evaluated in this patient group [162, 163].

- Anti-platelet therapy

  Anti-platelet therapy with either aspirin or clopidogrel is recommended as monotherapy in symptomatic PAD to reduce the risk for adverse CV events [164]. Its support in the literature is rather weak. Anti-coagulation therapy is not advised unless another indication is present. According to the European guidelines anti-platelet therapy should not be used for APAD patients [165].

- Anti-hypertensive treatment

    The optimal systolic blood pressure should target 135-145 mmHg and the diastolic 60-90mmHg [166] for reduction of CV events in PAD patients. The European Society of Hypertension guidelines proposes similar target blood pressures [167]. The first choice are Angiotensin-Converting-Enzyme inhibitors and Angiotensin Receptor Blockers, both known to signficantly reduce CV events in PAD [168]. Patients over 80 years with PAD, should also be prescribed anti-hypertensives [169].

- Anti-diabetic treatment

    Also in PAD patients with diabetes are metabolic control through anti-diabetic treatment advised, besides dietary recommendations [170]. Target HbA1C should be less than 7.0% to prevent microvascular complications [171]. For instance, the risk for hospitaliztion was five times lower for diabetic PAD patients when good glycemic controll (A1C<6%) was achieved as compared to those who didn't (A1C>7.5%) [172].

Screening

Screening for APAD by ABI measurements has been proposed, but there is currently insufficient scientific support for it [173]. Considering the high risk for CV events APAD patients face and a rather simple method to diagnose it, it can be considered a good candidate for screening programs. The main issue, however, with this concept is lack of proven cost-effective preventive treatments [174] [175], but it is also uncertain if ABI is as reliable as anticipated. Furthermore, it may be more reasonable to address a potential screening program to subgroups within the APAD population. One of the rationales for this thesis is to contribute to the basic information needed for designing a screening program for this group of patients.

Vascular surgery

Vascular surgical interventions are generally indicated to relieve leg symptoms, and are therefore never offered APAD patients, and only few with debilitating IC. CLI patients, on the other hand, have severe symptoms and their suffering weighs heavily in the careful risk-benefit analysis always performed before suggesting an intervention to a patient [20, 173]. The large proportion of patients with concomitant CV diseases and their often high age make this risk-assessment particularly important.

There is an abundance of surgical techniques available, which have evolved steadily since the beginning of the 1950[ies]. Examples of major break throughs are the discovery of heparin, the innovation of synthetic grafts, and endovascular techniques. Briefly, the main open procedures are endarterectomy -when the plaque dissected out of the affected artery – and bypass grafting. In the latter, blood flow is redirected around a blocked artery using a blood vessel from another part of the body or synthetic materials. For endovascular procedures a needle puncture enables access to the arterial system usually in the groin, through which inflatable balloons with and without stents are inserted under X-ray guidance. These are then used to open up the stenosed or blocked artery.

Who takes care of peripheral arterial disease?

In general, most patients with PAD are diagnosed and treated by general practitioners at primary care clinics[176]. Only patients with severe symptoms are referred to hospital-based vascular specialist care. Besides primary care physicians PAD patients are managed by several specialists, i.e. vascular surgeons, diabetologists, dermatologists, cardiologists, nephrologists, and orthopedic surgeons in an often rather fragmented health care process. Considering their high rate of concomitant diseases and need for preventive medication, they should ideally be managed by a vascular medicine specialist or angiologist and referred to other specialists only when necessary. Unfortunately, only few countries have enough vascular medicine specialists, and PAD patients use a variety of ways to receive their care. Another option that is available at some hospitals are management via vascular multidisciplinary teams. The lack of a consistent care pathways may contribute to the fact that many PAD patients are undertreated in terms of CV prevention.

Another circumstance that may influence the lack of preventive treatment is that many PAD patients with IC or even CLI present with vague or even absence of characteristic symptoms. APAD patients do not have any symptoms at all. Accordingly, there may be a knowledge gap about PAD among patients, and even parts of health care system, that is less common in CAD. For example, data from the Swedish National Registry for Vascular Surgery (Swedvasc) have reported variations between regions regarding implementation of best medical treatment and vascular interventions for this patient group.

SUMMARY OF KNOWLEDGE GAPS

Data on PAD epidemiology and contemporary natural history is limited and women are underrepresented in research studies. Although a continuous progress in CV treatment programs and important improvements in vascular surgical procedures have been established, in summarize, there are still large gaps of knowledge regarding

- the natural history of PAD, both in terms of the overall CV risk and the risk for detorioration of the affected limb.
- treatment patterns of PAD in relation to international guidelines.
- how to identify subjects with increased CV risk that would benefit of prophylacic measurses.
- which diagnostic method for PAD would be most suiteable to use in public health care.
- prevalence and impact of life-style risk factors in PAD
- efficacy of medical and lifestyle prophylactic treatment in PAD

RESEARCH AIMS

Overall aim

To determine the current national history and risk for CV events for different clinical stages of PAD.

Specific aims

The specific aims of each study in this research project were the following.

> **Study I**: to clarify the natural history in terms of mortality and assess contemporary risks in symptomatic and subclinical PAD.
>
> **Study II**: to describe CV and comorbitity outcome in different PAD severity stage groups and to present implementation of medical treatment according to international guidelines.
>
> **Study III**: to identify subgroups within the APAD population whose CV-risks are higher than other APAD subjects
>
> **Study IV**: to describe the consequences of different modes of calculating the ABI in terms of prevalence and risks for adverse CV-events.

MATERIALS AND METHODS

Brief methodology summary

Initially, a pilot study was performed in Solna in 2004, including 53 subjects, in order to enhance study design and dimensioning of study population and data collection methodology. The main study was launched in 2005, by performing a ten-year follow-up of a population-based cohort addressing the prevalence and natural history of PAD in Sweden [52]. At that time, a total of 8000 subjects from four different regions in Sweden were invited to participate. Primary data about comorbidity, PAD symptoms, risk factors and medication were obtained by questionnaires and physical examinations including bilateral ABI measurements. For follow-up in 2015, the same procedures were performed with additional data from The National Patient Register (NPR), The Cause of Death Register (CDR) and The Prescribed Drug Register (PDR).

Study design

Each study in the project was conducted as prospective observational cohort study on outcome, combining physical examinations and questionnaire data upon inclusion together with cross-linked register data for the whole observation period (Table 2).

In Paper I and II, the entire cohort was used with PAD severity stage groups according to symptoms and ABI levels. Data on associated comorbidity, risk factors, medication and mortality were collected from the NPR, the PDR and the CDR. Mortality rate and different causes of death were assessed for the different PAD groups.

In Paper II, medical therapies and to PAD associated comorbidity were assessed. The outcome was then compared between the different PAD groups.

In Paper III, the study population was restricted to the APAD subjects and references. The APAD subjects were subdivided according to presence of traditional major CV risk factors to elucidate the increased risk contributed by APAD. Outcome results were then described for fatal and non-fatal CV events according to presence of APAD and additional risk factors.

In Paper IV, the entire cohort was used. PAD was defined by an ABI<0.9 using two different calculation methods, which defined two different groups. Subjects with an ABI>0.9 according to both methods served as references. The PAD prevalence, mortality and risk for a CV event were

assessed for the different groups as were the power of ABI as a predictive tool for future CV event.

Table 2. Methodological overview for Paper I-IV

	Paper I	Paper II	Paper III	Paper IV
Design	Observational population-based cohort			
Exposure	APAD, IC, SLI	APAD, IC, SLI	APAD	ABI-HI, ABI-LO* (diagnostic method)
Data sources	Physical measurements, self-administered questionnaires and national registers			
Primary outcome	All-cause mortality	Cardiovascular and chronic comorbidity events	Cardiovascular events (fatal and non-fatal)	Cardiovascular events (fatal and non-fatal)
Secondary outcome	Different causes of mortality	Drug usage		CV event prediction by ABI
Setting	Multicenter in Sweden (Malmö, Älvkarleby, Karlstad and Bureå)			
Study period	January 13th 2005 until December 31th 2015			
Participants (n)	4950	5057	4659	4879
Statistical method	Frequency distribution and Cox regression	Frequency distribution and Cox regression	Frequency distribution and Royston-Parmar regression	Frequency distribution and Royston-Parmar regression, ROC and AUC, Kernel estimation for densities

APAD= Asymptomatic Peripheral Arterial Disease, IC=Intermittent Claudication, SLI=Severe Limb Ischemia

*Ankle Brachial Index (ABI) calculated by using the highest (HI) or lowest (LO) ankle blood pressure.

Cohort

The cohort was assembled between August 13th 2004 and January 13th 2005. The observation period lasted until December 31th 2015 when register data from the national registers covering 2004-2015 was retrieved.

To make the results generalizable for the Swedish population, four different demographic areas were chosen for inclusion. These were Karlstad (mid-sized city), Skellefteå (rural agricultural area), Malmö (large city with many immigrants) and Älvkarleby (rural industrial area). Some 2000 subjects at age 60-90 years were invited from each area.

Exclusion criterion were inability to confirm informed consent or dementia.

Data collection and methodology

The participants, were randomized from the Swedish tax register and invited by a letter, including three self-administered questionnaires. These questionnaires included data on concomitant diseases, smoking habits, pharmacological treatment and walking ability covering the questions in the Rose's World Health Organization (WHO) questionnaire [177] and the Walking Impairment Questionnaire (WIQ) [178, 179]. The first of these questionnaires addressed questions of length and height, followed by questions regarding comorbidity and duration of any smoking habits, complemented with questions on limb symptoms when walking or at rest and history of limb ulcers. The WIQ covers data on walking length, walking speed, ability to climb stairs, as well as other symptoms of significance for walking impairment such as sense of arrythmia, breathlessness and pain or limb cramps on a graded scale from 4 to 0.

After confirmation of informed consent to participate, the subjects were invited to their primary health care central where questionnaires were collated and physical examinations with ABI measurements were performed by specially trained nurses. All the study nurses had to attend courses covering PAD facts and pass examinations on theoretical and practical skills before study start. A coordinating study nurse did at several times visit the health care centers to monitor and validate the data collection procedure including the ABI measurements.

The ABI measurements were performed in a standardized manner. The brachial blood pressure was measured in the right arm using a 12 cm wide blood pressure cuff with the subject in a sitting position [180]. The ankle blood pressure was measured using a pocket CW-Doppler (8 MHz Doppler probe) and the same blood pressure cuff, with the subject lying on a bed, on his or her

back. The measurements were performed twice in each limb by insonating the posterior tibial and dorsal pedal arteries.

Subjects that were unable to visit the health care central were offered home visits to accomplish the examinations. Those who were diagnosed and considered at risk for CLI or had a brachial blood pressure above 180 mmHg were referred to their general practitioner.

Data was collated from the Swedish national health registers at the end of 2015, covering the whole observation period. From the CDR date and causes of death were retrieved as well as contributing causes. From the NPR, predefined health events according to specific chosen ICD-codes and dates within hospital-based care were collected.

A similar data collection was repeated in 2015 for the surviving cohort, although, for practical reasons, the number of references was reduced after power calculation.

Swedish national registers

Every Swedish citizen has a unique ten digits personal identity number. The Swedish government and the National Board of Health and Welfare holds several national high-quality registers, where the information of each subject is associated with the personal identity number which makes it possible to merge data for different registries. Data withdrawal is done by the National Board of Health and Welfare. It is then anonymized and delivered with the permission of an ethical board and the study participant.

The National Patient Register (NPR) includes all diagnoses recorded within Swedish hospitals both in inpatient care and in hospital based ambulatory care since 1984. Since 2001, the register also contains information on outpatient visits at hospitals. Beyond the primary discharge diagnosis, an unlimited number of secondary diagnoses can be recorded. The International Classification of Diseases, 10th revision (ICD-10) has been used for coding of diagnoses since 1997. The NPR is updated once a year and covers >99 % of all hospital discharges. The validity of the NPR has been shown to be high [181].

The Cause-of-Death Register (CDR) contains data on all deaths in Sweden since 1961. Data collected include time of death, underlying and contributing causes of death, in addition to about 30 other variables [182]. The use of CDR, in combination with NPR, has previously been demonstrated to provide highly accurate data in studies performed on similar patient

populations [183]. The validity of the CDR has been assessed [184] and was considered acceptable for epidemiological studies on common diseases.

The Prescribed Drug Register (PDR) was launched July 1, 2005. It comprises all purchases of prescribed drugs at pharmacies (dispensed drugs) and is updated each month. The register includes data on dispensed item (substance, formulation), dispensed amount, data of dispensing and the prescriber. All drugs are classified according to Anatomical Therapeutic Chemical (ATC) classification system. The PDR is considered an outstanding resource for assessing positive and negative effects of drug usage in large populations [185].

The Vascular Registry in Sweden (Swedvasc) is the world's oldest national vascular registry, collecting prospective data from all vascular surgery centers in Sweden since 1994. The registry has several times been validated regarding data accuracy [186]. In the Swedvasc, peri-procedural and follow-up data are collected for all vascular procedures performed in Sweden.

Definitions

In study I-III, the lowest systolic ankle blood pressure was used for the ABI calculation. In study IV, the highest and lowest ankle blood pressure were used for the ABI calculation.

In paper I and II, APAD was defined as an ABI<0.9 without qualifying answers in the questionnaires (i.e no pain in the calf or tights when walking). IC was defined as ABI<0.9 and qualifying answers in the questionnaires (i.e. leg pain when walking with relief at rest) and SLI was defined as an ankle blood pressure ≤70mmHg and >0mmHg. When pulse signal was undetectable in either the posterior tibial or dorsal pedal arteries, a record of missing data was made. SLI was used as a proxy for CLI [52], which was difficult to assess in an epidemiological study of this kind relying on questionnaire data. Subjects with normal ABI between 0.9 and 1.4 and no qualifying symptoms were classified as the Reference group (Ref).

In paper III, APAD was defined as an ABI<0.9 without qualifying answers for symptomatic PAD in the questionnaires, and subjects with an ABI≥0.9 and <1.4 served as references. The APAD subjects were then further subdivided according to presence of a risk factors as cardiac disease, stroke/TIA, diabetes, hypertension or smoking history.

In paper IV, PAD was defined as an ABI<0.9, calculated using the highest (ABI-HI) and lowest (ABI-LO) ankle blood pressure. Subjects were defined to be references or having PAD based on ABI-LO (Group 1) or ABI-HI (Group 2). Subjects with an ABI >0.9 and <1.4 according to

both methods were classified as references. Subjects with incompressible vessels (ABI>1.4) were excluded.

Outcome definitions are presented in each paper and were based on ICD-codes for each group of conditions or as self-reported information for baseline data. For assessments of pharmacological treatment, both self-reported information and data from the PDR were used. Drugs dispensed by pharmacies were recorded and used as a proxy for treatment. Information was collected for the following drug categories; platelet inhibitors, anticoagulation therapy, statins, anti-hypertensives and anti-diabetic drugs, which were, as described in each paper, classified according to the Anatomical Therapeutic Chemical (ATC) classification system and used for data retrieval.

Statistical methods

All statistical analyses were performed at the Centre of Clinical Research in Karlstad, Sweden. An overview is given in Table 2.

In Paper I, Kaplan-Meier plots were used to describe the mortality outcome by PAD stage. To compare the different groups, risk analyses were performed using Cox proportional hazard models with and without adjustments for age. Regression results were reported as hazard ratios (HR) with 95% confidence interval (CI). A cumulative incidence function curve was used to illustrate and compare different causes of mortality between baseline groups. Such curves are particularly useful when there is a relation of competing risks, as for different causes of mortality.

In Paper II, Cox proportional hazard models were used with adjustments for sex and baseline age and comorbidity. Venn diagrams were used for illustrations of affected vascular beds at baseline, separated by sex. Pharmacological treatment was described using drug prevalence plots, separated by PAD stage at baseline. To create these plots, drug observations were made in the PDR on weekly basis and divided by the momentary number of subjects in each stage group. Before presentation in paper II, the treatment plots were processed with calculations of average values to become smother rather than spiky. Finally, cumulative incidence function curves were used to illustrate different causes of death for the different PAD stages.

In Paper III, HR for CV events for APAD overall and with different risk factors present was calculated by using Royston-Parmar regression models. These were also used to investigate event risk (HR) for APAD and references with the same base-line risk factors adjusted for baseline age using a regression strategy. One advantage of the Royston-Parmar method is the

ability to incorporate time-dependent effects [187], which is useful in case the HR varies over the observation time.

In Paper IV, differences in the risk for a CV event between ABI groups were investigated with regression analyses (Cox and Royston-Parmar models) and Kaplan-Meier survival plots. Evaluation of predictive power of an ABI<0.9 was made with Receiver Operating Characteristic (ROC) curves and the Area Under the Curve (AUC).

In all studies, complete case analyses were performed since the overall prevalence of missing data was low. Multiple imputation methodology [188] was never considered necessary.

All analyses were carried out in Stata, StataCorp LP, College Station, Texas.

Ethical considerations

This project is conducted in harmony with the Helsinki declaration [189]. Our intention was to fill knowledge gaps, with a minimum of harm to the participants. With respect to the personal integrity of the participants, sensitive data were handled only by members of the research group, using only study-identification numbers and aggregated data. At inclusion, all included subjects were invited and informed by both written and oral information. They gave informed consent to participate and had the liberty to leave the study at any time. Risks for participants in this project were considered limited, i.e. mild discomfort while measuring the blood pressures and the workload of filling out questionnaires. The studies have been approved by the local ethics committees in Stockholm (KI 03-538 and Dnr 2014/2070-32), Umeå University (Dnr 03-459), Lunds University (832-0), Uppsala University (Dnr 03-564) and Örebro (Dnr 374-03).

RESULTS

PAPER I

Paper I presented long-term follow-up results on mortality for different PAD stages in a population-based setting. Also, age-adjusted risks for CV mortality were presented for subjects with different PAD stages and compared with the reference population. Finally, different causes of death were assessed. The composition of the study population at baseline, including mean age, is presented in Table 3 below.

Table 3. Prevalence of Peripheral Arterial Disease at inclusion separated by severity stage.

Stage group	N	Percent (%)	Mean age (years)
All	4940	100	71
Ref	4058	82	70
APAD	522	11	75
IC	295	6	76
SLI	65	1	78

APAD= Asymptomatic Peripheral Arterial Disease, IC=Intermittent Claudication, SLI=Severe Limb Ischemia

Figure 1 illustrates the finding of the trend of increasing all-cause mortality by PAD stage.

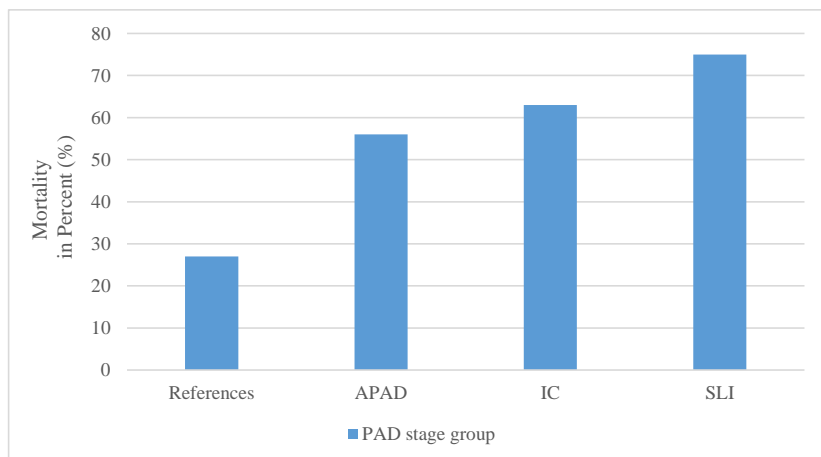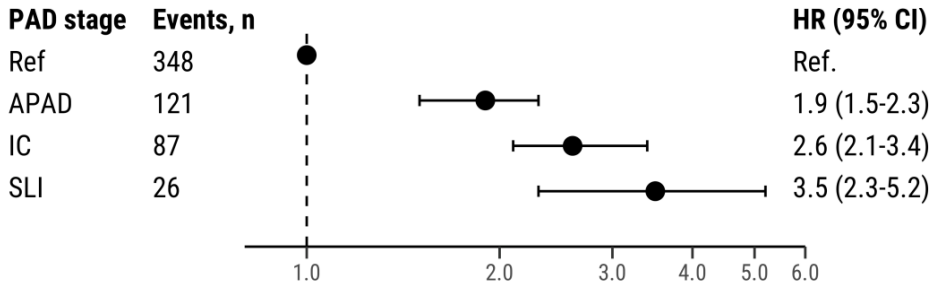**Figure 1. Ten years all-cause mortality by Peripheral Arterial Disease severity stage**

Table 4. Survivors by 2015 and mortality in percent.

PAD stage group	Year 2005	Year 2015	Mortality (%)
References	4058	2962	27
APAD	522	230	56
IC	295	109	63
SLI	65	16	75

APAD= Asymptomatic Peripheral Arterial Disease, IC=Intermittent Claudication, SLI=Severe Limb Ischemia

For all PAD subjects, the most common cause of death was an event from the CV disease area, responding for 45% of the deaths. Some 15% died of cancer and 6% of psychiatric and respiratory conditions, respectively. Since age was higher in symptomatic stage groups, analyses of risk for CV death were performed with adjustment of age (Figure 2).

Figure 2. Age-adjusted Hazard Ratio (HR) for cardiovascular death by Peripheral Arterial Disease (PAD) severity stage group

PAD stage	Events, n		HR (95% CI)
Ref	348		Ref.
APAD	121		1.9 (1.5-2.3)
IC	87		2.6 (2.1-3.4)
SLI	26		3.5 (2.3-5.2)

PAPER II

Paper II described to PAD associated comorbidity and pharmacological treatment patterns for men and women separated by different PAD stage groups. Our main results are summarized below.

1) Multiple comorbidity and polyvascular disease were common among PAD subjects. About one third of symptomatic subjects had an history of myocardial infarction and one quarter sufferd from diabetes mellitus at base line.

2) Treatment with antiplatelet therapy, statins and anti-hypertensive drugs was more common in PAD than references. At baseline, treatment with statins were recorded in 18% of APAD subjects, 30% in IC and 41% in SLI, compared to 15% of the references. By 2015, some 60% received pharmacological treatment according to international guidelines.

3) The risk for CV events and mortality has not improved for PAD subjects over the last decades.

4) Asymptomatic PAD subjects appeared to have almost similar risks for adverse CV events as symptomatic subjects.

5) Men were more often afflicted by myocardial infarction or stroke, while PAD was more common in women.

6) There was a tendency of a higher association to renal insuffecency for PAD subjects, (HR was 1.68 [1.18–2.31] in APAD).

7) The risk for developing diabetes were higher in PAD and escalating by PAD severity stage.

8) Cancer mortality was not increased in PAD.

PAPER III

Paper III was focused on APAD subjects, for identification of subgroups at higher CV risk. CV long term outcome was assessed and APAD subgroups were classified by presence of traditional CV risk factors at base line. The main results of this study are listed below.

1) In total did 56.2% of APAD subjects and 27.4% of references die during the observation time.

2) After adjustments for age and baseline comorbidities, the HR for CV mortality was 1.80 [1.45, 2.22, $p<0.001$] for APAD subjects.

3) The highest CV-risks were seen in APAD subgroups with either cardiac disease or diabetes (age-adjusted HR 2.54 [2.31-2.78] and 2.57 [2.28-2.89], respectively), which were even more prominent in women (HR 2.82 and 3.03).

4) The strongest impact of APAD upon other CV comorbitidty was observed in subjects with either diabetes mellitus, hypertension or a smoking history. For women with hypertension, the presence of APAD increased the HR by 1.86.

5) The most common cause of death was a CV-event.

Figure 3. Cumulative Mortality curves for Cardiovascular, Cancer, Psychiatric, Respiratory and Other mortality for References followed by Asymptomatic PAD.
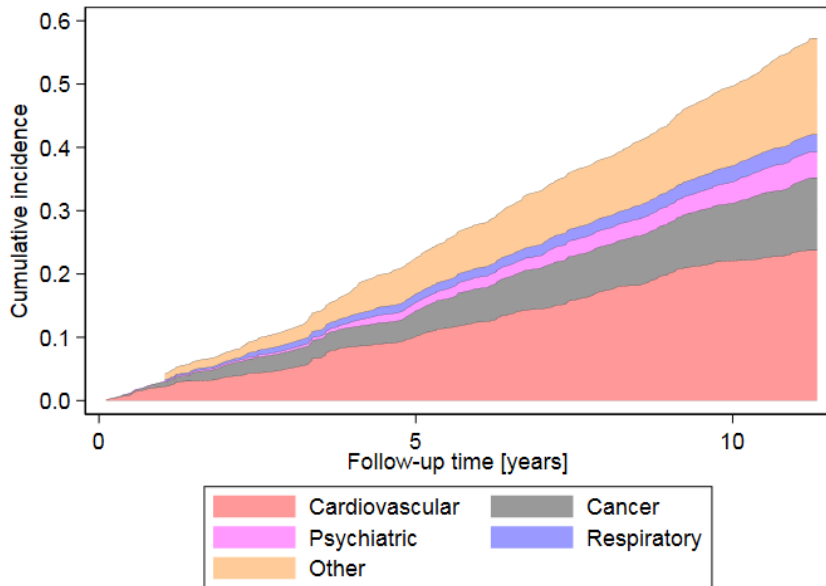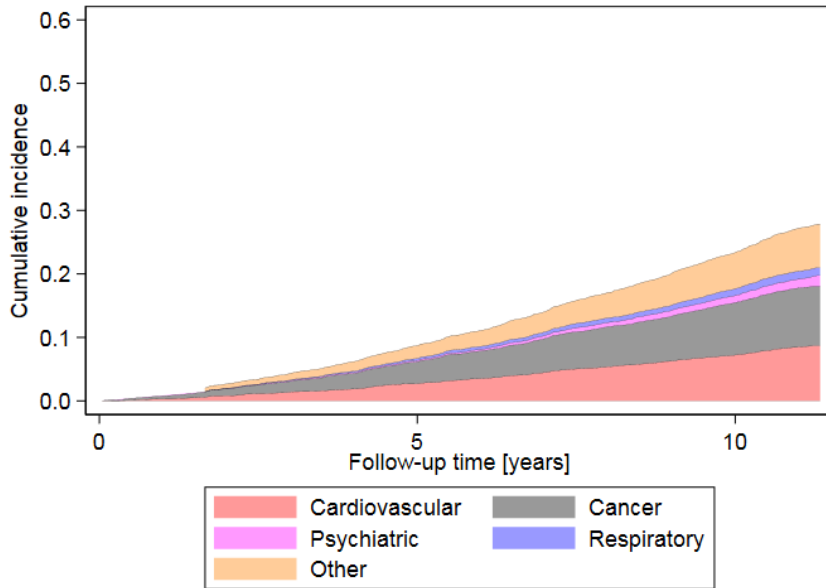
PAPER IV

Paper IV addressed the significance of a modified way to perform the ABI calculation to assess prevalence and the risk for adverse CV events and death in a population-based setting. The ABI-LO method was compared to ABI-HI. Some important differences were identified when using the different methods, as listed below.

1) The prevalence of PAD when using ABI-HI and ABI-LO was 9.6% (n=469) and 16.3% (n=799) respectively. Thus, the ABI-LO method identified 70% more subjects with PAD diagnosis.

2) The all-cause mortality after ten years was 67.2% for PAD when using ABI-HI, 48.8% when using ABI-LO and 27.6% for the references.

3) Both methods identified subjects with a significantly higher CV risk than the references. The age-adjusted HR (95% CI) for the composite outcome CV mortality and non-fatal CV events was 1.25 (1.06-1.49) and 2.11 (1.85-2.39) respectively for ABI-LO and ABI-HI.

4) The predictive ability of an ABI<0.9, defined by either method, to foresee a CV event was low.

Figure 4. Prevalence of PAD defined by having an ABI<0.9 according to the ABI-HI (red color only) and ABI-LO method (blue and red color together), divided by sex.
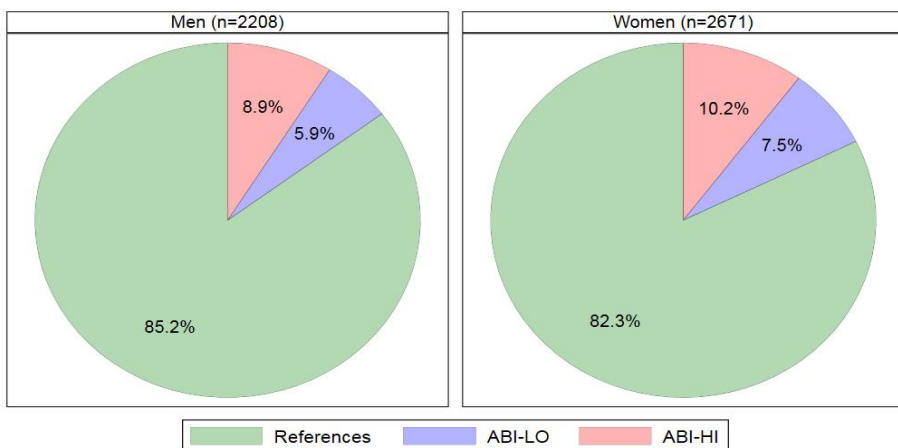
DISCUSSION

General discussion

Epidemiological research on disease development and risk factors usually relies on either a cohort or a case-control study design. While a cohort study in general is more time-consuming and costly to perform, it has the advantages of being particularly useful for common diseases and enable studies of multiple conditions with a minimum of bias. Furthermore, the results can be presented in terms of both relative and absolute risk. A case-control study design often has a retrospective approach and is focused on one condition, with results limited to relative risk or odds ratio. Over the last decades, the use of patient registers has escalated in clinical research and has become valuable for several reasons, for example the possibility to create large study populations with limited costs using national registers [190, 191]. Register-based research could easily be performed with long follow-up periods and with low impact of selection bias, although the quality of the information collected is strongly dependent of the quality and validity of the data in the register [192]. These circumstances enabled the study designs in this thesis and used a combination of a population-based cohort and validated national registers, providing high quality mortality and morbidity follow-up data during a long observation period.

The participants were initially invited in a manner that included a random selection from the general population in four different demographic areas in Sweden. The selection process of the cohort was important to reduce bias effects and to make the results generalizable to the entire Swedish population. Epidemiological research focusing on PAD is needed to fill gaps of knowledge. This project on natural history, treatment patterns and risk prediction for all PAD stages, was initiated to narrow some of these gaps, by providing applicable data when PAD subjects are diagnosed. It could also provide information for treatment guidelines as well as input for upcoming studies.

Prevalence of PAD

The prevalence of PAD is a key factor in studies evaluating the natural history, and changes greatly influence cohorts and morbidity. Under the twentieth century, however, it has been rather stable over time (Table 5). One report described a global prevalence increase by a modest 24% from 2000 to 2010 [193-195], due to changes in demographics. One explanation may

be that several factors in society have changed in parallel and the expanding number of the elderly has occurred simultaneous with improved prevention strategies. As age is one of the most important risk factors for PAD, it contributes strongly to an increasing prevalence. Previous studies on PAD epidemiology and natural history are by large outdated due to the demographic changes of the population - one rationale for this thesis. According to the Statistics Sweden, life expectancy for men and women have increased from 72.8 and 78.8 years to 80.3 and 84.0 years between 1980 and 2015 [196]. Other relevant changes affecting the PAD prevalence in the population, observed over the latest decades, are diminished smoking and an increased use of statins [197].

There are also several other circumstances that affect previous and contemporary prevalence data, such as the compositions of populations. Definitions of the disease may vary, and differences in age range, distribution of men and women, its socio-economic status are examples of this. In PAD, the inclusion of the PAD stage type is important. Likewise, influences the choice of diagnostic method for classification of disease the prevalence figures, such as the choice of ABI-HI or ABI-LO methods, that was addressed in Paper IV. One consequence of this is that studies on PAD prevalence are difficult to compare and evaluate. A large systemic review based on reports with PAD defined by ABI≤0.9, estimated prevalence in high- and low-income countries to vary between 3.54-24%. The most important factor for this variability was age group chosen [195].

Paper IV evaluated two different methods of calculating the ABI, and thus its ability to determine the prevalence but also how any differences in the cohorts based on this could influence risk. The ABI-LO method identified 70% more subjects at risk, but their average risk was lower when compared to the subjects identified with the ABI-HI method, which identified fewer subjects at risk. These differences are important to be aware of in further studies of screening. The ABI-LO method is also known to be more sensitive for diagnosis of PAD [218] than the standard way of performing the ABI. It may therefore be more favorable to use in CV risk stratification. The variations of measurement and calculation of the ABI leads to significant impact on prevalence. This will affect the clinicals, public health, and resource allocations, why a standardized methodology is warranted. Overall, accurate prevalence estimations are indeed essential for epidemiological research and the choice of ABI methodology needs to be considered when designing studies.

Table 5. Examples of key studies on prevalence of Peripheral Arterial Disease.

Study (Year)	Ages (years)	Type of cohort	Men/Women	Arm-BP method described	ABI-method described	Prevalence percent (%)
Edinburgh Artery Study [198] (1991)	55-74	Population-based	yes	yes	no	APAD 9.0% IC 4.5%
Rotterdam study [199] (1998)	55-106	Population-based	3105/4878	yes	ABI-LO	APAD 19% IC 1.6%
Strong Heart Study [200] (1999)	45-74	Native Americans	1720/2580	yes	Lower mean ABI-HI value	5.3% ABI<0.9
Vogt, Hulley [201] (1993)	65-93	Healthy women	0/1601	yes	no	2.9-15.5% depending on age
Swedish PAD Prevalence study [52] (2007)	60-90	Population-based	2301/2779	yes	ABI-LO	APAD 11% IC/SLI 8.2%
Multi-Ethnic Study of Atherosclerosis [202] (2002)	45-84	Population-based	3112/3458	yes	Lowest ABI-HI	ABI<0.9 3.7%
GET ABI study [203] (2004)	65-	Population-based	2864/3956	Yes	ABI-HI	ABI<0.9 18.0%
San Diego Population study [204] (2007)	29-91	Four ethnic groups	804/1539	Yes	ABI-HI	ABI≤0.9 4.4%

Ankle-brachial index methodology

The most central historic and current diagnostic method for epidemiological research in PAD is the ABI test. Variability in its application may strongly influence the results in epidemiological studies [205]. While usually regarded as a simple and reliable tool, there are still several problems related to its use. One example is how to measure the blood pressure, another the positioning of the subject while measuring [206], a third cuff size, the order of limb measurements and finally the method of pulse or blood flow detection. These problems have brought a debate whether it is sufficient to use single measurements or if repetitions are needed. Another discussion addresses

if the blood pressures should be measured uni- or bilaterally. As a consequence of this are many different protocols suggested, and an international working group was assembled to create unified recommendations regarding the key aspects of measurements of ABI and systolic blood pressure, as well as the calculation of ABI and the interpretation of ABI values. Their task also included CV risk assessments in APAD. Their report was published in 2012 [1], and recommended that the higher blood pressure obtained while insonating either the posterior tibial or the dorsal pedis artery should be divided by the higher of the right or left arm systolic blood pressure. In this thesis, we have tried to add information to this discussion, which would be available for an upcoming update of these recommendations. Our results indicate that the ABI-LO method could be preferred for CV-risk stratification purposes, while the standardized method might be more suitable for other diagnostics, for example before and after vascular surgery.

There are also several other factors affecting the ABI results more depending of the subject assessed. Examples are height, sex, and heart rate [207-209]. A physiological explanation of the ABI-test's weakness relates to the fact that the blood pressure wave amplifies as it travels in distal direction [210] and thus increases by the distance. Therefore, height may impact on the ABI-result in by giving higher blood pressures in taller subjects. The differences seen in ABI for men and women may therefore be related to such differences in average height. Specific ABI thresholds for men and women have been suggested but is not yet evaluated nor established. Any influence of body shape on the interpretation of ABI is even more complex to elucidate, since obesity and associated diabetes are both are important risk factors for PAD, and therefore difficult to separate between methodological problems with the blood pressure and true effects of associated morbidity [211].

The significance of a high ABI, defined by a threshold >1.4, appears to be associated with increased mortality [212] and is more common among subjects with diabetes [213], but is only evaluated in a few studies [214, 215]. It may be due to increased vascular stiffness [216]. In Paper IV, 42 subjects, or 0.9 %, of the subjects enrolled, had an ABI>1.4. They were excluded from further analysis in this thesis but could be focus for another study in the future. For instance, it is unclear what this group's risk for CV events is and if they were included in our study cohort would have affected the results. Considering their small number, it is unlikely it would have changed our results greatly.

In the physical data collection, it was common that pressure measurements were approximated to the closest 5 or 10 mmHg. More important was that an undetectable ankle pulse was considered as missing data and not as ankle blood pressure of 0 mmHg, which may have

influenced the size and outcome for stage group with the most severe disease. In our cohort 23 subjects had missing data due to an undetectable ankle pulse.

Overall, an ABI≤0.9 has a specificity of 83-99% and an accuracy of 72-89% for detection of a stenosis ≥50% [217]. Sensitivity may vary, especially in diabetes and elderly subjects, but an ABI≤0.9 has now become widely used cut-off value to define PAD prevalence and for risk assessment [93]. In Paper IV, we evaluated the predictive ability for an individual of having an ABI<0.9 and found it to be low. This was not an unexpected, but noteworthy since it rarely is described in the scientific literature. Another clinically useful finding was that a normal ABI (>0.9) implies a strong negative predictive value for CV risk, i.e. men had a 95% probability of not developing a CV-event within one year and women 97%. The corresponding figures after three years was and 83% and 90% (Figure 5).

Figure 5. Results of ABI-LO<0.9 and ABI-HI<0.9 abilities to predict a fatal or non-fatal cardiovascular event for men and women described by Positive Predictive Value (PPV) and Negative Predictive Value (NPV).
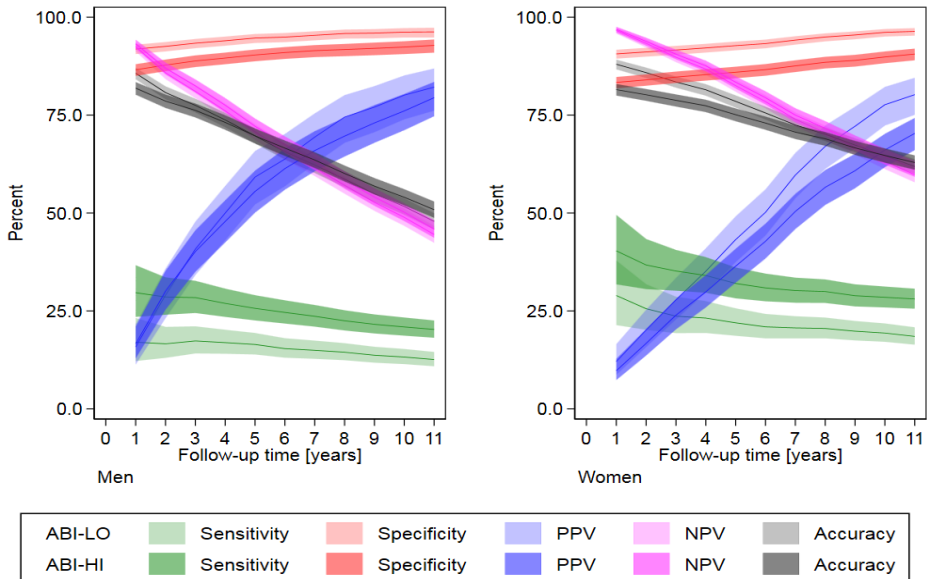
Modifiable risk factors and global trends

As for most atherosclerotic diseases, one of the strongest concomitant risk factors in PAD is diabetes mellitus. Its incidence is rising worldwide [218, 219] and today close to half a billion people are living with diabetes. This number is also expected to rise by 25 % by 2030 and over 50% by 2045 [220]. Diabetes mellitus and development of atherosclerosis are connected through several biochemical pathways, including chronic inflammation, disturbed lipid metabolism, hyperglycemia, insulin resistance and oxidative stress [104]. Adequate glycemic control remains the most important treatment strategy to prevent manifestations of atherosclerosis in diabetic patients. Novel strategies to achieve this include prescription of sodium glucose cotransporter-2 (SGLT-2) inhibitors that have been shown to be effective in reducing CV mortality in type 2 diabetes [221]. In our cohort baseline prevalence of diabetes was 17% in PAD subjects compared to 10% in references. By the end of the observation period more than 25% of symptomatic PAD subjects were using antidiabetic treatment, which was twice as common as in the reference group. Recently, sex differences in concomitant occurrence of diabetes and PAD was evaluated and found a similar risk for diabetic men and women [222]. In Paper III, we noted that the combination of having APAD and diabetes conveyed a particularly high risk for having a future CV event, particularly among women. This observation indicates that we need to be even more attentive to patients having this combination, and perhaps should strive for precise preventive measures for this group.

Similar trends for hypertension is reported, with a strong incidence increase especially in low- and middle-income countries [223]. The presence of hypertension drives the atherosclerotic process, as the development of PAD, probably through disturbing endothelial function and inducting oxidative stress [224]. In the present cohort 47% of the PAD subjects were identified with hypertension at baseline. By 2015, 90% of IC subjects were using antihypertensive medication, highlighting that hypertension is the most common modifiable risk factor in this patient group. Today, there are abundant of drugs available for anti-hypertensive treatment so it can be individualized to achieve the goals of blood pressure lowering. As for diabetes, the finding of PAD and hypertension should encourage us to be more aggressive when it occurs (Paper III), and it may be possible that this combination even would warrant a specific treatment strategy.

Dyslipidemia in PAD was not evaluated in this thesis. Nevertheless, dyslipidemia is one of the most important modifiable risk factors in PAD [107, 199, 225, 226] and is considered attributable to one third of global ischemic heart disease according to the WHO [227]. A tendency of a decreasing blood lipid levels is observed in some high-income countries, but not globally [228]. Despite

available evidence of risk reduction, 70 % of IC subjects in our cohort received statin treatment by 2015.

Another risk factor that is increasing rapidly is obesity. Between 1975 and 2014, the global prevalence of obesity increased from three to 11% in men and from six to 15% in women [229]. In the present cohort, 13% of the subjects with PAD was obese at baseline. The mechanisms of obesity to influence on atherosclerotic development and PAD are probably multifactorial, with features of disturbed lipid metabolism, insulin resistance and chronic inflammation [230]. Obesity was not the focus of this thesis but may have influenced its findings by influencing ABI measurements (see above) besides its impact as a general risk factor.

Tobacco smoking reduction strategies are implemented in many countries and between 2000 and 2010 smoking trends have declined in many countries worldwide [231]. Target goals regarding tobacco usage has been achieved by 21%, so there is room for continuous improvement. To quit smoking is probably the most cost-effective intervention to reduce development of atherosclerosis and PAD [232], and also to reduce the risk for a CV event in PAD patients. This was again enforced by the findings in Paper III in this thesis.

Life-style risk factors such as smoking, obesity and low physical activity were common in our cohort with PAD but was not the main focus of this thesis. In a separate baseline analysis of all the 957 PAD subjects in this cohort, we assessed the prevalence of the risk factors, smoking (defined as having any previous or ongoing self-reported smoking history by each subject), obesity (defined by having a Body Mass Index >30 kg/m^2 (BMI)) and a low physical activity. For the latter, we used a proxy for low physical activity, the Walking Impairment Questionnaire (WIQ) [179], and defined the risk factor of low physical activity, called Low WIQ index, as having a self-reported score within the lowest quartile from the WIQ results among the responses from the total cohort of references and PAD subjects.

In our PAD cohort, the most common life-style risk factor noted at base line was smoking (52%), followed by a Low WIQ index (41%). Only a smaller part had obesity (13%). The prevalence of none, one, two or three of these lifestyle dependent CV-risk factors were in PAD subjects 18%, 41%, 26% and 5%, respectively. The prevalence was independent of age. At least 73% of the males and 66% of the females had at least one life-style dependent CV risk factor, for which they should be offered treatment and support from health care services (Figure 6). The majority of men with PAD and either obesity or Low WIQ index were smokers.

In summary, together with a longer life expectancy, the trends for increasing incidences of the important risk factors to develop PAD indicate that the PAD population could grow world-wide

in the near future. Possibly this could be counteracted by declining smoking habits, blood pressure control and healthier blood lipid levels in some countries. However, continued and perhaps even increased awareness of this condition and associated risk factors is warranted. The latter includes more general recognition of this disease, both in terms of investigating symptomatic disease, liberal use of ABI-measurements, and high suspicion of PAD in patients with an unclear presentation. It is likely that a more frequent use of ABI measurements in primary care settings is one way to achieve this and could result in better management. A dedicated care process driven in concordance with some of the findings of this thesis, including aggressive lifestyle and pharmacological treatment, is likely to improve the rather dismal natural history of PAD.

Figure 6. Relationship of prevalence of the lifestyle risk factors (LRF) in PAD in percent (%). Smoking history, obesity (BMI>30) and subjects within the lowest quartile of the Walking Impairment Questionnaire (Low WIQ) at baseline 2005 separated by sex.
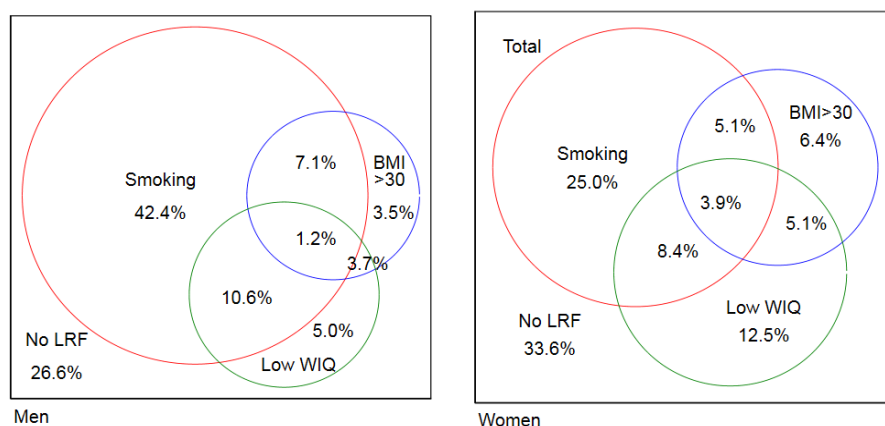
Mortality and morbidity

One main finding in this thesis is that the HR for CV mortality in PAD varies between 1.9 to 3.5, depending on PAD stage. This finding implies a lack of reduction in CV-risk for PAD subjects, when compared to studies performed decades ago [3, 5, 82]. While other manifestations of atherosclerosis such as CAD or CVD have declining mortality rates [54, 55], this was not observed in our PAD cohort. Studies I and II are, as far as we know, unique for being the only large population-based long-term observational studies on CV outcome and drug usage in PAD,

including asymptomatic subjects. One of the most well-cited reports on PAD outcome, published in 1992, presented a relative CV mortality of 6.6 in PAD, when compared to a reference population in which other CV diseases had been excluded [2]. Other key observational studies on PAD are listed in Table 1. In Paper I of this thesis, different causes of death were analysed and revealed that 45% of the PAD subjects had a CV event as a main cause of death and 64% had a CV condition as one of the contributing causes to death. As mentioned previously, this implies a remaining strong need of improved PAD awareness and optimized CV prophylactic treatment. One rationale for Paper I was to update the rather dated information of all-cause and CV mortality in PAD, given the growing demographic patterns of more elderly over the latest decades. Moreover, pharmacological prevention treatment possibilities have also evolved with time. In light of this, it was surprising that the risk patterns appear to be steady in our study as compared to many older ones.

In Paper II, the comorbidity burden in all PAD stages was dominated by CV disease, both when counting fatal and non-fatal events. Men were more affected than women by myocardial infarction and stroke and died at younger ages than women. While PAD was more common in women, men had more fatal events. The dominance of PAD in women may be explained by competing risks, meaning that death excluded other incident events including PAD. In contrast to other studies [233, 234], the cancer comorbidity and mortality was not increased in our PAD subjects, most probably for the same reason. In the literature, there are support for associations between PAD and some forms of cancer, in particular pulmonary, head and neck, and urinary tract malignancies. The explanation may be common risk factors [235, 236]. Another explanation for a low frequency of cancer mortality for our PAD subjects may be dependent on less successful CV prophylactic treatment in PAD, meaning CV-mortality was not enough prevented in PAD to alter the cause of death towards cancer mortality.

In Paper I, the risk analysis was made with and without adjusting for age. The explanation for this has two specific explanations. The first was to present real-life results, comprehensible for care providers and useful in common clinical practice and for doctor-patient interactions. The reason was to make our results comparable with previously presented data that may have a different cohort composition with other average ages.

The follow up used in this thesis for all four studies had the ambition to assess the PAD morbidity progress over time. To achieve this, data was collated from questionnaires, national registers on survival and vascular intervention after over ten years, in 2015. To save resources a reduction of the reference group was made for physical examinations and ABI measurements, but all surviving subjects with PAD at base line was followed up. A summary of invited subjects

and participants in the cohort who were examined at different timepoints are presented in Figure 7.

Figure 7. Included subjects for the follow-up analysis by 2015.

Declaration of patient data:

Included 2004	Invited 2015	Participants 2015
Subgroups year 2004: results	Subgroups year 2015 Invited	Participants year 2015: results
Ref group: N=4198 (83 %)	Reduced Ref group: N=871	Ref group N= 486 (61%)
APAD: N=522 (10 %)	APAD: 50 % mortality => 261 alive	APAD: N= 143 (18 %)
IC: N=295 (6 %)	IC: 59% mortality => 121 alive	IC: N=73 (9%)
SLI: N=65 (1 %)	SLI: 72% mortality => 18 alive	SLI: N=97 (12 %)
		51 Subj excluced due to vascular Op
Total Participants N=5076	Invited subjects N= 1271	Total participants N= 799

Fifty-one subjects had undergone a vascular intervention during the observation period and were excluded from further analysis. Among the PAD subjects, over 50% died during the observation time, which was the main reason for the decreasing numbers of subjects in the cohort. Other reasons for non-participation at the ten-year follow up is presented in Table 6 below.

The focus of this thesis was the natural history of the morbidity facing the patient at base line. The data gathered also included the fate of limb symptoms, but this has not yet been fully analyzed. Classification of surviving subjects into the PAD stage groups was also repeated at follow up after ten years to identify shifts between the groups during the observation time. The analyses also included change over time in individual ABI values, walking distance and walking speed. The latter two was derived from Walking Impairment Questionnaire scores. Briefly, while not fully analyzed, 32 % of the APAD stage group, became symptomatic, but only 14 % of the refences. As much as 31% of IC subjects deteriorated to the SLI stage. APAD subjects, in comparison to the reference population, had a substantial risk for progression to symptomatic disease in both in terms of walking ability and deterioration of ABI. One third of APAD subjects moved to a more severe PAD stage. The mortality rates in the symptomatic groups were high. Other reports evaluating disease progression in PAD have reported similar results [237, 238].

Table 6. Invited subjects and reasons for non-participation in physical assessments in follow-up by 2015.

Participation status 2015	Men n (%)	Women n (%)	Total n (%)
Participating	354 (70.8)	494 (64.3)	848 (66.9)
Dead	21 (4.2)	31 (4.0)	52 (4.1)
Moved out	14 (2.8)	29 (3.8)	43 (3.4)
Dementia	5 (1.0)	15 (2.0)	20 (1.6)
Terminal disease	2 (0.4)	1 (0.1)	3 (0.2)
Feeling well	0 (0.0)	3 (0.4)	3 (0.2)
Uninterested	34 (6.8)	83 (10.8)	117 (9.2)
Could not be contacted	15 (3.0)	27 (3.5)	42 (3.3)
Declined to participate	21 (4.2)	34 (4.4)	55 (4.3)
Participating, but no data	34 (6.8)	51 (6.6)	85 (6.7)
Totalt	500 (100)	768 (100)	1268 (100)

Asymptomatic PAD – a mixed population with diverse risk levels

APAD is a rather modern concept in the literature and a less understood manifestation than IC [239]. The scientific interest for this condition is growing since it is associated with similar CV risk as IC, despite its lack of symptoms [239]. As mentioned previously, Paper III showed that APAD together with any one of other traditional CV risk factor significantly increased the CV risk further by a HR of 1.2-2.0, dependent on the risk factor studied. This finding supports that the large asymptomatic subgroup is heterogenous and contains subjects facing a variety of levels of CV-risk. To find a tool, able to discriminate those who are exposed to a high risk from those who are not, would be very valuable. One application of such tool could be for screening purposes.

One suggestion is to distinguish between active or inactive APAD subjects, defined by the ability or inability to walk the distance of six blocks [27]. Inactive APAD subjects may have a low overall functional performance capacity due to other comorbidities and therefore never experience exertional leg symptoms and therefore missed by health care practitioners. They might therefore face a very high risk due to a heavier disease burden, than more ambulatory

subjects[240]. Because of the size of the APAD group and the hidden high-risk group with low mobility, the economic burden on society of APAD could be higher than costs for subjects with IC [241].

To our knowledge, Paper III is the largest population-based report on APAD outcome from 2005 until today. This study was originally designed to identify subgroups within APAD that could be suitable for studies on screening activities and subsequent treatment with concomitant analyses of cost-effectiveness. While a general screening for APAD is not yet proven cost-effective, we believe that the data from this thesis warrants actual screening studies for APAD in sub-populations with either hypertension, diabetes or smoking, combined with interventions with prophylactic measures. While APAD per se is a significant CV risk factor, the impact of APAD varies within its population. Screening activities could first become cost-effective in populations with higher risks. As expected, in our cohort the highest CV risks was observed in subjects with both APAD and cardiac disease. Interestingly, the strongest impact on CV risk dependent on APAD prevalence, was seen in subjects with hypertension, smoking or diabetes, three groups less exposed to CV prophylactic treatment than the patients with ischemic heart disease. In women with hypertension and no other risk factor, presence of APAD the HR was 1.86 for an adverse CV event.

Pharmacological treatment

One main question when initiating this thesis project was to elucidate if the increasing use of preventive pharmacological treatment has reduced the risk for CV events also in PAD patients. Intervention with drugs to reduce this risk has strong support in the literature.

Lipid-lowering agents, for instance, have become the most important group of drugs used for treatment in PAD. Through large-scale randomized trials, statins have been shown to reduce the risk of major CV-events by 25% for each mmol/L reduction in LDL cholesterol during each year of usage [242] (Table 7). Treating 10 000 patients with atorvastatin 40mg daily for five years with the indication of primary or secondary prevention can avoid 500 and 1000 major CV events [242]. It costs only about 2£ per month for each patient. Statins' mechanisms involve reducing the cholesterol biosynthesis in the liver by inhibiting the HMG-CoA enzyme. They also have antiatherogenic effects independent of the hypolipidemic action [243], which is attributed to anti-inflammatory properties [155]. Ten percent of patients do not tolerate statins due to side-effects such as myalgia, derangement in liver function and diabetogenic effects [244]. Also, for PAD patients the beneficial effects of statins are the reduction of adverse CV events, including also

amputations and improved walking ability. If LDL target levels not are reached with statins in PAD patients, adding ezetimide [245] or a PCSK-9 inhibitor [162] is recommended. In Paper II, the proportion of patients using statins was rather low over the ten-year observation time they were followed, despite strong evidence. The indication used preventive drug treatment, for example detection of PAD or any other CV event, was not known when performing the analysis. While the findings of undertreatment therefore must be interpreted with caution due to methodological issues, it still indicates room for improvement.

Contrary to lipid-lowering, the scientific support for anti-platelet therapy is rather weak in PAD (Table 6) and only has some scientific support in symptomatic disease. The strongest evidence for aspiring used comes from the Antithrombotic Triallists Collaboration [246]. In the CAPRIE trial, clopidogrel is recommended over aspirin [247]. Two recently published studies, covering PAD populations, support the use of oral anti-coagulation therapy in combination with anti-platelet therapy in high-risk patients. Such regimen, however, has to be balanced to the risk of bleedings, which did occur in these two studies (HRs, as compared to patients without anti-coagulation was 1.49 [248] and HR 1.42 [249]). In our cohort anticoagulation was quite common and increased over time. Supposedly, most of the patients were prescribed anticoagulation for other indications than PAD, which may be the preferred approach considering the rather low support especially for APAD patients.

In patients with hypertension and symptomatic PAD, angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers have both shown to reduce major adverse CV events and amputations [250-252] and are therefore recommended as first line therapy in patients with PAD symptoms and concomitant hypertension [165].

Table 7. Examples of key studies on drug treatment for cardiovascular risk reduction of importance in treatment of Peripheral Arterial Disease.

Study (year)	Subjects (n)	Drug	Study design	End-points	Risk reduction
Anti-platelet therapy					
Antithrombotic Trialists' Collaboration [246] (2002)	135,000	various anti-platelet drugs	meta-analysis of RCT	MACE	Odds reduction (SE) 23% (8)
Berger, Hiatt [253] (2009)	5,269	aspirin	meta-analysis of RCT	MACE, bleeding	Non-significant for CV-events
Catalano, Peto [254] (2007)	366	aspirin, anti-oxidants	double-blinded RCT	MACE	HR 0.42, 95% CI 0.21-0.83
CAPRIE [247] (1996)	19,185	clopidogrel vs aspirin	blinded RCT	MACE	Clopidogrel more effective than aspirin (RR 8.7%)
Aspirin for Asymptomatic Atherosclerosis Trialists [255] (2010)	28,980	aspirin	RCT	CV-event, revascularising	Non-significant
POPADAD trial [256] (2008)	1,276	aspirin, anti-oxidants	double-blinded RCT	CV event, amputation	Non-significant
Lipid-lowering agents					
Heart Protection Study [257] (2007)	20,536	simvastatin	RCT	MACE	RR 22% (95% CI 15-29)
Gencer, Sabatine [160] (2020)	244,090	various lipid lowering drugs	meta-analysis of RCT	MACE	RR 26% (p=0.0019)
JUPITER [258] (2008)	17,802	rosuvastatin	double-blinded RCT	MACE	HR 0.56 (p<0.00001)
IMPROVE-IT [245] (2015)	18,144	ezetimide	double-blinded RCT	MACE	RR 6.4% (p=0.016)
LIPID [259] (1998)	9,014	pravastatin	double-blinded RCT	CV mortality	RR 24% (p<0.001)
FOURIER [260] (2017)	27,564	evolocumab	double-blinded RCT	MACE	HR 0.85 (p<0.001)

Anti-hypertensive therapy					
HOPE Study [252] (2000)	9,500	ramipril	double-blinded RCT	MACE	RR 22% (p<0.0001)
ONTARGET [251] (2008)	8,576	telmisartan vs ramipril	double-blinded RCT	MACE	equivalent effect
Anti-coagulation therapy					
VOYAGER-PAD [249] (2020)	6,564	rivaroxaban	double-blinded RCT	MACE, limb events, bleeding	HR 0.85 (p=0.009)
COMPASS Trial [248] (2020)	27,395	rivaroxaban	double-blinded RCT	CV events, bleeding	HR 0.80 (p=0.0005)

MACE (Major Adverse Cardiovascular Event), CV (Cardiovascular), RCT (Randomized Controlled Trial), HR (Hazard Ratio), RR (Relative Risk)

In this cohort, 60% of the symptomatic PAD subjects received pharmacological treatment including a combination of platelet inhibition or anticoagulation therapy, statins, and antihypertensive treatment when hypertension was present at follow up. As mentioned, this was an increase from 20% in 2005. Unfortunately, we did not draw blood samples at base line due to lack of resources and was therefore unable to assess if target levels and blood lipids were achieved. While we have a single arm blood pressure at base line and follow up, we were not able to link blood pressure prescriptions to individual events over the observation time. While not a part of this thesis, we are considering to access primary care data, to perform additional analysis of our blood pressure data and drug usage in our cohort in the future.

One important aspect concerning the assessment of optimized drug treatment in PAD relates to uncertainties in diagnosing PAD in primary care, so applicable also for this thesis. One implication of this issue is that we did not know how many of the subjects that were classified as symptomatic in the study previously and had sought for PAD symptoms at primary care clinics but not received treatment. This may partly explain the result in our cohort of undertreatment of symptomatic PAD but did not reduce the actual number of subjects in need of treatment.

In spite of having a higher one-year mortality than those surviving a myocardial infarction [261], symptomatic PAD patients have repeatedly been shown to be using less statins and anti-platelet therapies than subjects with CAD [262, 263]. In revascularized PAD subjects, where the evidence

for anticoagulation is stronger, a large Danish observational cohort study recently presented implementation of therapy guidelines and compliance for drugs in PAD subjects, which also had led to a reduction of adverse CV events. Even so, less than 40% of treatment-naïve subjects initiated cardioprotective therapy after revascularization in that study [264]. There are other support for improvements such as similar study from Italy [265]. As noted above, we did not see a noteworthy improvement over time in our cohort, but this may both be due to methodological problems as well as that the final assessment of the patients now dates a few years back.

In summary, our PAD subjects appear to be undertreated in general, and there is room for improvement in line with what is recommended in the literature [266-270]. One issue related to this is the fact that a majority of PAD subjects in society do not undergo vascular surgery, and therefore remains undetected. Increased awareness in primary care setting could be one way to address this.

Methodological aspects

There are always potential issues in cohort studies of this kind, and the choice of methodology can always be questioned. As PAD is a common condition in populations over 60 years and is affected by many risk factors, a longitudinal observational cohort study is a suitable model to use when studying outcome and risk factors. The length of the study period was chosen to catch events over a rather long time, and the time period of ten years was probably adequate for identifying significant outcome differences. Longer follow up would cause more events to be analyzed but would contain few subjects at the end of the observation period. Moreover, the combination of physical examinations and questionnaire-, as well as register data, minimized losses-to-follow up enabling meaningful long-term follow-up. The data quality of Swedish national registers is validated and considered reliable. CDR in combination with NPR, for example, has been demonstrated to provide highly accurate data in similar patient populations [183]. In accordance with this, the cohort used in thesis was on the whole able to demonstrate significant differences in outcome data confirming adequate dimensioning of sample size at base line. Another strength was that the cohort was population-based with randomized participants from four different demographic areas in Sweden. Nevertheless, are there always alternative methodological choices that could have been chosen. This could have avoided the lack of quality data on pharmacological treatment over time in this thesis, as well as providing sufficient information of treatment goals and lifestyle factors.

Another interesting study-model considered in the beginning of this project was a totally register-based model for Paper I and II. This could have been possible through using ICD-codes for intermittent claudication and PAD for inclusion of subjects from the NPR. The advantage of such a study model would have been the possibility to cover the whole Swedish population over more than ten years. A similar study design was recently published for IC subjects [271]. This model, however, would lose the advantage of being population-based and including the APAD subjects. The latter were the reasons for not selecting it for the studies in this thesis.

Clinical implications of the findings in this thesis

The scientific literature [272] with support from the findings in this thesis implies that subjects over 60 years of age, with at least one concomitant CV risk factor, should undergo ABI assessment. For calculating the ABI, the lowest ankle blood pressure should be used and if the ABI is found to be <0.9 or >1.4 interventions should be initiated. Such should include both life-style recommendations and CV prophylactic drug treatment to reduce the overall CV risk.

This suggestion is motivated by scientific data supporting it, as well as demographic changes and progression of health care. Over the last two decades major improvements in public health and CV outcome have been accomplished [273]. Improved access to medical care and management of hypertension, diabetes and secondary prevention have reduced the occurrence of CV events [274]. This has contributed to an increasing elderly population that needs to be considered when planning for new interventions [93]. Many studies on treatments covered mainly younger populations why additional information on its impact on elderly is needed. Offering more prophylactic treatment to elderly can be considered controversial because their comorbidities and risk for drug interactions [275]. Recent studies have reported beneficial effects of lipid lowering [160] and hypertension treatment in elderly [169], supporting aggressive treatment. Moreover, enhanced therapeutic strategies also need information on its cost-effectiveness.

More intense treatment strategies should also be evaluated considering a global perspective and socio-economic status. For low-income societies, the WHO has formulated the "best buys" regarding prevention of non-communicable diseases, of which the CV area is dominating [276]. The WHO recommendations include measures to reduce tobacco and alcohol use, increased taxation on food products rich on fat, sugar and salt, support to physical activity and provision of healthy meals to school children, as the initial choice of intervention. For societies with a high GDP drug treatment is likely to be indicated early in the PAD disease course.

CONCLUSIONS

Paper I Mortality risks are more than doubled in symptomatic PAD patients compared with reference subjects and increase by severity of PAD stage. Among all PAD subjects, CV causes were the most common main cause of death (45%) and a CV event was present as either the main or one of the three most common contributing causes of death in 64% of the cases.

Paper II Asymptomatic PAD subjects confer similar risk for CV events as symptomatic patients. PAD is more common in women, but men face a higher risk for death and CV events. The risk for other comorbidity as diabetes, non-fatal myocardial infarction and stoke and renal failure was doubled in PAD. Some 60% of symptomatic PAD subjects received prophylactic drugs according to guidelines by 2015.

Paper III Subjects with APAD and any other common CV risk factor have significantly higher risks for CV events than those without APAD. The strongest impact of APAD on CV risk was noted in subjects with hypertension, diabetes and smoking. ABI measurements should be considered an important indication for aggressive multifactorial risk factor reduction in populations with any other prevalent CV risk factor.

Paper IV When using the ABI-LO method more subjects at risk were identified, but their average risk was lower when comparing to the ABI-HI method which identified less subjects at risk. These differences are important to be aware of in further studies of screening. The predictive value of ABI measurements was low.

POINTS OF PERSPECTIVE

Future aspects

Many patients with PAD in this cohort were identified with lifestyle risk factors and lacked medical treatment according to guidelines. Whether the responsibility for these patients' treatment should be addressed to vascular clinics, performing vascular surgery, or general practitioners is not clear and may vary dependent on symptomatic severity of the disease. The access to facilities for provision of secondary prevention, such as supervised training, smoke-stopping advisory and the knowledge of optimized medical treatment may also vary. These circumstances are all likely to contribute to poor treatment implementation why they need to be investigated for identification of what impedes provision of optimized treatment. A first step in such an investigation could be to invite vascular surgery clinics and primary health care centrals in Sweden in a survey, performed with either interviews or questionnaires, to capture possible obstacles in treatment implementation. The questions in the survey could for example address issues like whom is considered responsible for the medical treatment, if analyses of lipids and long-term glucose levels are performed before and after initiation of therapy, and if supervised training and smoke stop interventions with follow-ups are a part of the clinics' practice, etcetera. Such a primary evaluation of treatment practices would be valuable before further addressing issues with therapy implementation and the findings may advocate for allocation of more resources to health care for PAD subjects, to make it possible for specialists to provide primary and secondary prevention according to guidelines.

Based on the findings in this thesis it is tempting to pursue ABI screening to identify a population that are at risk, that is modifiable with interventions. Currently the evidence for this is insufficient but as a next step in such attempts, it may be reasonable to focus upcoming studies on subgroups of the populations with either hypertension, diabetes or smoking history. These populations are, when PAD is identified with an ABI<0.9, exposed to an almost doubled risk for mortality or a CV-event, and this group is unlikely to receive adequate treatment today. As a suggestion to evaluate this concept is to invite citizens with hypertension or diabetes, in the age range of 60-70 years, for a randomized trial with ABI-measurements as a lead in to enrollment, who should receive either an optimized prophylactic drug treatment regimen or current best medical practice. Statins, for example, should definitely be a part of such regimen, being one of the most cost-effective intervention available to health systems [114] and motivated even in low risk populations. With well-defined primary outcome parameters, such as CV-events and

mortality, follow-up could be register-based, using the NPR, CDR and PDR. Secondary outcome variables could address lifestyle parameters and ambulation ability. Such a trial would, thus be focused on primary prevention in a cohort largely composed by APAD subjects.

The optimal drug regimen used in a treatment trial in PAD could also be addressed in upcoming studies. Anti-coagulation strategies, for instance, needs to be evaluated also in APAD, and new drugs could have a place in mild PAD for prevention. One other example is PCSK-9 inhibitors that have a powerful lipid-lowering effect and appear effective in reduction of CV risks [161, 277], but its use may be accompanied by side effects making it unsuitable for secondary prevention in this patient group. Of course needs the cost-effectiveness of any new drugs be considered for a potential screening and intervention situation.

Another type of drug, the SGLT-2 inhibitors, could be used in new drug regimens for prevention directed to a diabetic population. They are a quite recent addition to the treatment arsenal of diabetes type 2 , showing promising results in reducing CV-events [278]. This class of drugs are still controversial in PAD [279] and its effects needs to be evaluated. One controversy relates to the findings in the CANVAS trial [280], where the frequency of lower limb amputations were doubled in patients treated with SGLT-2 inhibition as compared to those who didn't receive this drug. Since both the diabetes incidence and indications for prescribing SGLT-2 inhibitors are growing, it is possible that this class of drugs could have a place also in PAD subjects.

As an alternative to offer new drugs to a regimen, established drugs could be employed in an APAD or similar population. One example is the so called "polypill", designed to improve compliance and adherence to a reasonable cost for subjects with low to average CV risk. The polypill is designed for primary prevention and consists of a fixed dose of combinations of anti-platelet therapy, statins and ACE-inhibition, but is not yet evaluated in western populations [281, 282].

Not to forget, the large improvements reported for Swedish CV-morbidity between 1986-2002, were mainly due to lifestyle changes. In that risk factor modelling analysis, two thirds of the improvements were attributable to lifestyle risk factors and one third to new drug treatments [283]. There is still room for life-style improvements for many patients and current recommendations must be continuously maintained and encouraged. Finding the optimal way to support patients to success in compliance to medication and lifestyle modification is the aim of an ongoing trial [284].

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REFERENCES

1.   Aboyans V, Criqui MH, Abraham P, et al. Measurement and Interpretation of the Ankle-Brachial Index. *Circulation* 2012; 126: 2890-2909. DOI: doi:10.1161/CIR.0b013e318276fbcb.

2.   Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 1992; 326: 381-386. DOI: 10.1056/NEJM199202063260605.

3.   Leng GC, Lee AJ, Fowkes FG, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1996; 25: 1172-1181. 1996/12/01. DOI: 10.1093/ije/25.6.1172.

4.   Newman AB, Shemanski L, Manolio TA, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. *Arterioscler Thromb Vasc Biol* 1999; 19: 538-545.

5.   Heald CL, Fowkes FG, Murray GD, et al. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: Systematic review. *Atherosclerosis* 2006; 189: 61-69. DOI: 10.1016/j.atherosclerosis.2006.03.011.

6.   Thompson RC, Allam AH, Lombardi GP, et al. Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations. *Lancet* 2013; 381: 1211-1222. 2013/03/16. DOI: 10.1016/S0140-6736(13)60598-X.

7.   Brown RA, Shantsila E, Varma C, et al. Current Understanding of Atherogenesis. *Am J Med* 2017; 130: 268-282. 2016/11/27. DOI: 10.1016/j.amjmed.2016.10.022.

8.   Ross R and Glomset JA. The pathogenesis of atherosclerosis (first of two parts). *The New England journal of medicine* 1976; 295: 369-377. 1976/08/12. DOI: 10.1056/nejm197608122950707.

9.   Ross R and Glomset JA. The pathogenesis of atherosclerosis (second of two parts). *The New England journal of medicine* 1976; 295: 420-425. 1976/08/19. DOI: 10.1056/nejm197608192950805.

10.   Ronak Delewi MHY, MsC; John Kastelein, MD, PhD. TEXTBOOK of CARDIOLOGY.ORG part of cardionetworks.org. 2012: 2.1.

11.   Bergheanu SC, Bodde MC and Jukema JW. Pathophysiology and treatment of atherosclerosis : Current view and future perspective on lipoprotein modification treatment. *Neth Heart J* 2017; 25: 231-242. DOI: 10.1007/s12471-017-0959-2.

12.   Katakami N. Mechanism of Development of Atherosclerosis and Cardiovascular Disease in Diabetes Mellitus. *Journal of atherosclerosis and thrombosis* 2018; 25: 27-39. 2017/09/29. DOI: 10.5551/jat.RV17014.

13.   Alexander RW. Hypertension and the Pathogenesis of Atherosclerosis. *Hypertension* 1995; 25: 155-161. DOI: doi:10.1161/01.HYP.25.2.155.

14.   Ambrose JA and Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: An update. *Journal of the American College of Cardiology* 2004; 43: 1731-1737. DOI: https://doi.org/10.1016/j.jacc.2003.12.047.

15.   Tarbell J, Mahmoud M, Corti A, et al. The role of oxygen transport in atherosclerosis and vascular disease. *Journal of The Royal Society Interface* 2020; 17: 20190732. DOI: doi:10.1098/rsif.2019.0732.

16.   VanderLaan PA, Reardon CA and Getz GS. Site Specificity of Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2004; 24: 12-22. DOI: doi:10.1161/01.ATV.0000105054.43931.f0.

17.   DeBakey ME, Lawrie GM and Glaeser DH. Patterns of atherosclerosis and their surgical significance. *Ann Surg* 1985; 201: 115-131. DOI: 10.1097/00000658-198502000-00001.

18.   Mortality GBD and Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1459-1544. DOI: 10.1016/S0140-6736(16)31012-1.

19.   Fischer U, Baumgartner A, Arnold M, et al. What Is a Minor Stroke? *Stroke* 2010; 41: 661-666. DOI: doi:10.1161/STROKEAHA.109.572883.

20.   Aboyans V, Ricco J-B, Bartelink M-LEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *European Heart Journal* 2017; 39: 763-816. DOI: 10.1093/eurheartj/ehx095.

21.   Anderson EA and Mark AL. Flow-mediated and reflex changes in large peripheral artery tone in humans. *Circulation* 1989; 79: 93-100. 1989/01/01. DOI: 10.1161/01.cir.79.1.93.

22.   Heil M, Eitenmüller I, Schmitz-Rixen T, et al. Arteriogenesis versus angiogenesis: similarities and differences. *Journal of Cellular and Molecular Medicine* 2006; 10: 45-55. DOI: https://doi.org/10.1111/j.1582-4934.2006.tb00290.x.

23.   Cooke JP and Meng S. Vascular Regeneration in Peripheral Artery Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2020; 40: 1627-1634. DOI: doi:10.1161/ATVBAHA.120.312862.

24.   Koutakis P, Ismaeel A, Farmer P, et al. Oxidative stress and antioxidant treatment in patients with peripheral artery disease. *Physiol Rep* 2018; 6: e13650. 2018/04/04. DOI: 10.14814/phy2.13650.

25.   Brass EP and Hiatt WR. Acquired skeletal muscle metabolic myopathy in atherosclerotic peripheral arterial disease. *Vasc Med* 2000; 5: 55-59. 2000/03/29. DOI: 10.1177/1358836x0000500109.

26.   Pizzimenti M, Riou M, Charles A-L, et al. The Rise of Mitochondria in Peripheral Arterial Disease Physiopathology: Experimental and Clinical Data. *J Clin Med* 2019; 8: 2125. DOI: 10.3390/jcm8122125.

27.   McGrae McDermott M, Greenland P, Liu K, et al. Leg Symptoms in Peripheral Arterial DiseaseAssociated Clinical Characteristics and Functional Impairment. *JAMA* 2001; 286: 1599-1606. DOI: 10.1001/jama.286.13.1599.

28.   Creager MA, Matsushita K, Arya S, et al. Reducing Nontraumatic Lower-Extremity Amputations by 20% by 2030: Time to Get to Our Feet: A Policy Statement From the American Heart Association. *Circulation* 2021: Cir0000000000000967. 2021/03/26. DOI: 10.1161/cir.0000000000000967.

29.   Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007; 45 Suppl S: S5-67. DOI: 10.1016/j.jvs.2006.12.037.

30.   McDermott MM, Greenland P, Liu K, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. *JAMA* 2001; 286: 1599-1606. 2001/10/05. DOI: 10.1001/jama.286.13.1599.

31.   Shu J and Santulli G. Update on peripheral artery disease: Epidemiology and evidence-based facts. *Atherosclerosis* 2018; 275: 379-381. 2018/05/22. DOI: 10.1016/j.atherosclerosis.2018.05.033.

32.   Weinberg I and Jaff MR. Nonatherosclerotic Arterial Disorders of the Lower Extremities. *Circulation* 2012; 126: 213-222. DOI: doi:10.1161/CIRCULATIONAHA.111.060335.

33.   Davis DD and Shaw PM. Popliteal Artery Entrapment Syndrome. *StatPearls*. Treasure Island (FL): StatPearls Publishing

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34.   Peterson JJ, Kransdorf MJ, Bancroft LW, et al. Imaging Characteristics of Cystic Adventitial Disease of the Peripheral Arteries: Presentation as Soft-Tissue Masses. *American Journal of Roentgenology* 2003; 180: 621-625. DOI: 10.2214/ajr.180.3.1800621.

35.   Fontaine R, Kim M and Kieny R. [Surgical treatment of peripheral circulation disorders]. *Helv Chir Acta* 1954; 21: 499-533. 1954/12/01.

36.   Suggested standards for reports dealing with lower extremity ischemia. Prepared by the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery. *J Vasc Surg* 1986; 4: 80-94. 1986/07/01.

37.   Novo S, Coppola G and Milio G. Critical Limb Ischemia: Definition and Natural History. *Current drug targets Cardiovascular & haematological disorders* 2004; 4: 219-225. DOI: 10.2174/1568006043335989.

38.   Hardman RL, Jazaeri O, Yi J, et al. Overview of classification systems in peripheral artery disease. *Semin Intervent Radiol* 2014; 31: 378-388. DOI: 10.1055/s-0034-1393976.

39.   Dormandy JA and Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg* 2000; 31: S1-S296.

40.   Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 2007; 33 Suppl 1: S1-75. DOI: 10.1016/j.ejvs.2006.09.024.

41.   Mills JL, Sr., Conte MS, Armstrong DG, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIfI). *J Vasc Surg* 2014; 59: 220-234 e221-222. 2013/10/16. DOI: 10.1016/j.jvs.2013.08.003.

42.   Taylor GI and Palmer JH. The vascular territories (angiosomes) of the body: experimental study and clinical applications. *Br J Plast Surg* 1987; 40: 113-141. 1987/03/01. DOI: 10.1016/0007-1226(87)90185-8.

43.   van Reijen NS, Ponchant K, Ubbink DT, et al. Editor's Choice - The Prognostic Value of the WIfI Classification in Patients with Chronic Limb Threatening Ischaemia: A Systematic Review and Meta-Analysis. *Eur J Vasc Endovasc Surg* 2019; 58: 362-371. 2019/06/25. DOI: 10.1016/j.ejvs.2019.03.040.

44.   Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of High and Low Ankle Brachial Index to All-Cause and Cardiovascular Disease Mortality. *Circulation* 2004; 109: 733-739. DOI: doi:10.1161/01.CIR.0000112642.63927.54.

45.   Shabani Varaki E, Gargiulo GD, Penkala S, et al. Peripheral vascular disease assessment in the lower limb: a review of current and emerging non-invasive diagnostic methods. *Biomed Eng Online* 2018; 17: 61. 2018/05/13. DOI: 10.1186/s12938-018-0494-4.

46.   Schroder F, Diehm N, Kareem S, et al. A modified calculation of ankle-brachial pressure index is far more sensitive in the detection of peripheral arterial disease. *J Vasc Surg* 2006; 44: 531-536. 2006/09/05. DOI: 10.1016/j.jvs.2006.05.016.

47.   Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013; 382: 1329-1340. 2013/08/07. DOI: 10.1016/S0140-6736(13)61249-0.

48.   Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation* 2011; 123: e18-e209. 2010/12/17. DOI: 10.1161/CIR.0b013e3182009701.

49.   Creager MA, Belkin M, Bluth EI, et al. 2012 ACCF/AHA/ACR/SCAI/SIR/STS/SVM/SVN/SVS Key data elements and definitions for peripheral atherosclerotic vascular disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to develop Clinical Data Standards for peripheral atherosclerotic vascular disease). *J Am Coll Cardiol* 2012; 59: 294-357. 2011/12/14. DOI: 10.1016/j.jacc.2011.10.860.

50.   Selvin E and Erlinger TP. Prevalence of and Risk Factors for Peripheral Arterial Disease in the United States. *Circulation* 2004; 110: 738-743. DOI: doi:10.1161/01.CIR.0000137913.26087.F0.

51.   Kohn CG, Alberts MJ, Peacock WF, et al. Cost and inpatient burden of peripheral artery disease: Findings from the National Inpatient Sample. *Atherosclerosis* 2019; 286: 142-146. 2019/06/07. DOI: 10.1016/j.atherosclerosis.2019.05.026.

52.   Sigvant B, Wiberg-Hedman K, Bergqvist D, et al. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *J Vasc Surg* 2007; 45: 1185-1191. DOI: 10.1016/j.jvs.2007.02.004.

53.   Organization WH. Cardiovascular diseases. 2020.

54.	Herrington W, Lacey B, Sherliker P, et al. Epidemiology of Atherosclerosis and the Potential to Reduce the Global Burden of Atherothrombotic Disease. *Circ Res* 2016; 118: 535-546. DOI: 10.1161/CIRCRESAHA.115.307611.

55.	Muller-Nordhorn J, Binting S, Roll S, et al. An update on regional variation in cardiovascular mortality within Europe. *Eur Heart J* 2008; 29: 1316-1326. DOI: 10.1093/eurheartj/ehm604.

56.	Vancheri F, Backlund L, Strender L-E, et al. Time trends in statin utilisation and coronary mortality in Western European countries. *BMJ Open* 2016; 6: e010500. DOI: 10.1136/bmjopen-2015-010500.

57.	Sundaram V, Bloom C, Zakeri R, et al. Temporal trends in the incidence, treatment patterns, and outcomes of coronary artery disease and peripheral artery disease in the UK, 2006–2015. *European Heart Journal* 2019; 41: 1636-1649. DOI: 10.1093/eurheartj/ehz880.

58.	Bjorck L, Rosengren A, Bennett K, et al. Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. *Eur Heart J* 2009; 30: 1046-1056. DOI: 10.1093/eurheartj/ehn554.

59.	Vyas MV, Mrkobrada M, Donner A, et al. Underrepresentation of peripheral artery disease in modern cardiovascular trials: systematic review and meta-analysis. *Int J Cardiol* 2013; 168: 4875-4876. DOI: 10.1016/j.ijcard.2013.07.050.

60.	Stanhewicz AE, Wenner MM and Stachenfeld NS. Sex differences in endothelial function important to vascular health and overall cardiovascular disease risk across the lifespan. *Am J Physiol Heart Circ Physiol* 2018. DOI: 10.1152/ajpheart.00396.2018.

61.	Hiramoto JS, Katz R, Weisman S, et al. Gender-specific risk factors for peripheral artery disease in a voluntary screening population. *J Am Heart Assoc* 2014; 3: e000651-e000651. DOI: 10.1161/JAHA.113.000651.

62.	Mathur P, Ostadal B, Romeo F, et al. Gender-Related Differences in Atherosclerosis. *Cardiovascular Drugs and Therapy* 2015; 29: 319-327. DOI: 10.1007/s10557-015-6596-3.

63.	Mazhari R and Hsia J. Prevalence, clinical significance, and management of peripheral arterial disease in women: is there a role for postmenopausal hormone therapy? *Vasc Health Risk Manag* 2005; 1: 111-117. DOI: 10.2147/vhrm.1.2.111.64084.

64.	McDermott MM, Greenland P, Liu K, et al. Sex differences in peripheral arterial disease: leg symptoms and physical functioning. *Journal of the American Geriatrics Society* 2003; 51: 222-228. 2003/02/01. DOI: 10.1046/j.1532-5415.2003.51061.x.

65.	Caro J, Migliaccio-Walle K, Ishak KJ, et al. The morbidity and mortality following a diagnosis of peripheral arterial disease: long-term follow-up of a large database. *BMC Cardiovasc Disord* 2005; 5: 14. DOI: 10.1186/1471-2261-5-14.

66.	Zhou ZY, Liu YK, Chen HL, et al. HbA1c and Lower Extremity Amputation Risk in Patients With Diabetes: A Meta-Analysis. *Int J Low Extrem Wounds* 2015; 14: 168-177. 2015/07/02. DOI: 10.1177/1534734615593190.

67.	Thiruvoipati T, Kielhorn CE and Armstrong EJ. Peripheral artery disease in patients with diabetes: Epidemiology, mechanisms, and outcomes. *World J Diabetes* 2015; 6: 961-969. DOI: 10.4239/wjd.v6.i7.961.

68.	Bourrier M, Ferguson TW, Embil JM, et al. Peripheral Artery Disease: Its Adverse Consequences With and Without CKD. *Am J Kidney Dis* 2020; 75: 705-712. 2019/12/28. DOI: 10.1053/j.ajkd.2019.08.028.

69.	Garg PK, Biggs ML, Carnethon M, et al. Metabolic syndrome and risk of incident peripheral artery disease: the cardiovascular health study. *Hypertension (Dallas, Tex : 1979)* 2014; 63: 413-419. 2013/11/04. DOI: 10.1161/HYPERTENSIONAHA.113.01925.

70.	Vidula H, Liu K, Criqui MH, et al. Metabolic syndrome and incident peripheral artery disease - the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis* 2015; 243: 198-203. 2015/09/24. DOI: 10.1016/j.atherosclerosis.2015.08.044.

71.	Beauchamp G, Lassonde J, Laurendeau F, et al. Lung cancer and peripheral vascular surgery. *Can J Surg* 1983; 26: 472-474. 1983/09/01.

72.	Terzikhan N, Lahousse L, Verhamme KMC, et al. COPD is associated with an increased risk of peripheral artery disease and mortality. *ERJ Open Res* 2018; 4: 00086-02018. DOI: 10.1183/23120541.00086-2018.

73.	Hsu WY, Lin CL and Kao CH. A Population-Based Cohort Study on Peripheral Arterial Disease in Patients with Schizophrenia. *PLoS One* 2016; 11: e0148759. 2016/02/13. DOI: 10.1371/journal.pone.0148759.

74.	Newman AB, Fitzpatrick AL, Lopez O, et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. *J Am Geriatr Soc* 2005; 53: 1101-1107. 2005/08/20. DOI: 10.1111/j.1532-5415.2005.53360.x.

75.	Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; 364: 937-952. 2004/09/15. DOI: 10.1016/S0140-6736(04)17018-9.

76.	O'Doherty MG, Cairns K, O'Neill V, et al. Effect of major lifestyle risk factors, independent and jointly, on life expectancy with and without cardiovascular disease: results from the Consortium on Health and Ageing Network of Cohorts in Europe and the United States (CHANCES). *European Journal of Epidemiology* 2016; 31: 455-468. DOI: 10.1007/s10654-015-0112-8.

77.	Rippe JM. Lifestyle Strategies for Risk Factor Reduction, Prevention, and Treatment of Cardiovascular Disease. *Am J Lifestyle Med* 2018; 13: 204-212. DOI: 10.1177/1559827618812395.

78.	Sakamoto S, Yokoyama N, Tamori Y, et al. Patients With Peripheral Artery Disease Who Complete 12-Week Supervised Exercise Training Program Show Reduced Cardiovascular Mortality and Morbidity. *Circulation Journal* 2009; advpub: 0811170155-0811170155. DOI: 10.1253/circj.CJ-08-0141.

79.	Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *The New England journal of medicine* 2013; 368: 1279-1290. 2013/02/26. DOI: 10.1056/NEJMoa1200303.

80.	Roth GA, Johnson C, Abajobir A, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol* 2017; 70: 1-25. 2017/05/22. DOI: 10.1016/j.jacc.2017.04.052.

81.	Daoud EM, Ramadan MM, El-Shahhat N, et al. Associations of symptomatic or asymptomatic peripheral arterial disease with all-cause mortality and cardiovascular mortality. *The Egyptian Heart Journal* 2011; 63: 7-12. DOI: https://doi.org/10.1016/j.ehj.2011.08.022.

82.	Hooi JD, Kester AD, Stoffers HE, et al. Asymptomatic peripheral arterial occlusive disease predicted cardiovascular morbidity and mortality in a 7-year follow-up study. *J Clin Epidemiol* 2004; 57: 294-300. DOI: 10.1016/j.jclinepi.2003.09.003.

83.	Newman AB, Tyrrell KS and Kuller LH. Mortality over four years in SHEP participants with a low ankle-arm index. *J Am Geriatr Soc* 1997; 45: 1472-1478. 1997/12/24. DOI: 10.1111/j.1532-5415.1997.tb03198.x.

84.	Jelnes R, Gaardsting O, Hougaard Jensen K, et al. Fate in intermittent claudication: outcome and risk factors. *Br Med J (Clin Res Ed)* 1986; 293: 1137-1140.

85.	Lassila R, Lepantalo M and Lindfors O. Peripheral arterial disease--natural outcome. *Acta Med Scand* 1986; 220: 295-301.

86.	Sigvant B, Lundin F and Wahlberg E. The Risk of Disease Progression in Peripheral Arterial Disease is Higher than Expected: A Meta-Analysis of Mortality and Disease Progression in Peripheral Arterial Disease. *Eur J Vasc Endovasc Surg* 2016; 51: 395-403. 2016/01/19. DOI: 10.1016/j.ejvs.2015.10.022.

87.	Dhaliwal G and Mukherjee D. Peripheral arterial disease: Epidemiology, natural history, diagnosis and treatment. *The International journal of angiology : official publication of the International College of Angiology, Inc* 2007; 16: 36-44. DOI: 10.1055/s-0031-1278244.

88.	Smolderen KG, Zitteren Mv, Jones PG, et al. Long‐Term Prognostic Risk in Lower Extremity Peripheral Arterial Disease as a Function of the Number of Peripheral Arterial Lesions. *Journal of the American Heart Association* 2015; 4: e001823. DOI: doi:10.1161/JAHA.115.001823.

89.   Alberts MJ, Bhatt DL, Mas JL, et al. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. *Eur Heart J* 2009; 30: 2318-2326. DOI: 10.1093/eurheartj/ehp355.

90.   Melillo E, Micheletti L, Nuti M, et al. Long-term clinical outcomes in critical limb ischemia--A retrospective study of 181 patients. *Eur Rev Med Pharmacol Sci* 2016; 20: 502-508.

91.   Diehm C, Allenberg JR, Pittrow D, et al. Mortality and Vascular Morbidity in Older Adults With Asymptomatic Versus Symptomatic Peripheral Artery Disease. *Circulation* 2009; 120: 2053-2061. DOI: doi:10.1161/CIRCULATIONAHA.109.865600.

92.   Kornitzer M, Dramaix M, Sobolski J, et al. Ankle/arm pressure index in asymptomatic middle-aged males: an independent predictor of ten-year coronary heart disease mortality. *Angiology* 1995; 46: 211-219. DOI: 10.1177/000331979504600304.

93.   Criqui MH and Aboyans V. Epidemiology of Peripheral Artery Disease. *Circulation Research* 2015; 116: 1509-1526. DOI: doi:10.1161/CIRCRESAHA.116.303849.

94.   Berger JS, Hochman J, Lobach I, et al. Modifiable risk factor burden and the prevalence of peripheral artery disease in different vascular territories. *J Vasc Surg* 2013; 58: 673-681.e671. 2013/05/07. DOI: 10.1016/j.jvs.2013.01.053.

95.   Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; 295: 180-189. 2006/01/13. DOI: 10.1001/jama.295.2.180.

96.   Kullo IJ and Leeper NJ. The Genetic Basis of Peripheral Arterial Disease. *Circulation Research* 2015; 116: 1551-1560. DOI: doi:10.1161/CIRCRESAHA.116.303518.

97.   Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2224-2260. 2012/12/19. DOI: 10.1016/s0140-6736(12)61766-8.

98.   Willigendael EM, Teijink JA, Bartelink ML, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. *J Vasc Surg* 2004; 40: 1158-1165. 2004/12/29. DOI: 10.1016/j.jvs.2004.08.049.

99.   Clark D, 3rd, Cain LR, Blaha MJ, et al. Cigarette Smoking and Subclinical Peripheral Arterial Disease in Blacks of the Jackson Heart Study. *Journal of the American Heart Association* 2019; 8: e010674. 2019/01/24. DOI: 10.1161/jaha.118.010674.

100.   Lu JT and Creager MA. The relationship of cigarette smoking to peripheral arterial disease. *Rev Cardiovasc Med* 2004; 5: 189-193. 2004/12/08.

101.   Heitzer T, Brockhoff C, Mayer B, et al. Tetrahydrobiopterin improves endothelium-dependent vasodilation in chronic smokers : evidence for a dysfunctional nitric oxide synthase. *Circ Res* 2000; 86: E36-41. 2000/02/10. DOI: 10.1161/01.res.86.2.e36.

102.   FREEMAN DJ, GRIFFIN BA, MURRAY E, et al. Smoking and plasma lipoproteins in man: effects on low density lipoprotein cholesterol levels and high density lipoprotein subfraction distribution. *European Journal of Clinical Investigation* 1993; 23: 630-640. DOI: https://doi.org/10.1111/j.1365-2362.1993.tb00724.x.

103.   Pittilo RM, Clarke JM, Harris D, et al. Cigarette smoking and platelet adhesion. *British journal of haematology* 1984; 58: 627-632. 1984/12/01. DOI: 10.1111/j.1365-2141.1984.tb06109.x.

104.   Poznyak A, Grechko AV, Poggio P, et al. The Diabetes Mellitus-Atherosclerosis Connection: The Role of Lipid and Glucose Metabolism and Chronic Inflammation. *Int J Mol Sci* 2020; 21: 1835. DOI: 10.3390/ijms21051835.

105.   Jude EB, Oyibo SO, Chalmers N, et al. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes care* 2001; 24: 1433-1437. 2001/07/27. DOI: 10.2337/diacare.24.8.1433.

106.   O'Keefe JH, Carter MD and Lavie CJ. Primary and secondary prevention of cardiovascular diseases: a practical evidence-based approach. *Mayo Clin Proc* 2009; 84: 741-757. DOI: 10.1016/S0025-6196(11)60525-9.

107.	Aday AW and Everett BM. Dyslipidemia Profiles in Patients with Peripheral Artery Disease. *Curr Cardiol Rep* 2019; 21: 42-42. DOI: 10.1007/s11886-019-1129-5.

108.	Lawes CM, Vander Hoorn S and Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet (London, England)* 2008; 371: 1513-1518. 2008/05/06. DOI: 10.1016/s0140-6736(08)60655-8.

109.	Makin A, Lip GY, Silverman S, et al. Peripheral vascular disease and hypertension: a forgotten association? *Journal of human hypertension* 2001; 15: 447-454. 2001/07/21. DOI: 10.1038/sj.jhh.1001209.

110.	Arinze NV, Gregory A, Francis JM, et al. Unique aspects of peripheral artery disease in patients with chronic kidney disease. *Vasc Med* 2019; 24: 251-260. 2019/03/03. DOI: 10.1177/1358863x18824654.

111.	Gal D, Thijs B, Glänzel W, et al. Hot topics and trends in cardiovascular research. *European Heart Journal* 2019; 40: 2363-2374. DOI: 10.1093/eurheartj/ehz282.

112.	(NCCDPHP) NCfCDPaHP. Health and Economic Costs of Chronic Diseases. 2020.

113.	Group WCRCW. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *Lancet Glob Health* 2019; 7: e1332-e1345. 2019/09/07. DOI: 10.1016/S2214-109X(19)30318-3.

114.	Collaborators GBDCoD. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392: 1736-1788. DOI: 10.1016/S0140-6736(18)32203-7.

115.	Casey S, Lanting S, Oldmeadow C, et al. The reliability of the ankle brachial index: a systematic review. *J Foot Ankle Res* 2019; 12: 39. 2019/08/08. DOI: 10.1186/s13047-019-0350-1.

116.	Crawford F, Welch K, Andras A, et al. Ankle brachial index for the diagnosis of lower limb peripheral arterial disease. *Cochrane Database Syst Rev* 2016; 9: CD010680. 2016/09/15. DOI: 10.1002/14651858.CD010680.pub2.

117.	Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *European Heart Journal* 2003; 24: 987-1003. DOI: 10.1016/s0195-668x(03)00114-3.

118.	Canepa M, Fonseca C, Chioncel O, et al. Performance of Prognostic Risk Scores in Chronic Heart Failure Patients Enrolled in the European Society of Cardiology Heart Failure Long-Term Registry. *JACC: Heart Failure* 2018; 6: 452-462. DOI: https://doi.org/10.1016/j.jchf.2018.02.001.

119.	Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97: 1837-1847. 1998/05/29. DOI: 10.1161/01.cir.97.18.1837.

120.	D'Agostino RB, Sr., Grundy S, Sullivan LM, et al. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001; 286: 180-187. 2001/07/13. DOI: 10.1001/jama.286.2.180.

121.	Ankle Brachial Index C, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008; 300: 197-208. 2008/07/10. DOI: 10.1001/jama.300.2.197.

122.	Velescu A, Clara A, Penafiel J, et al. Adding low ankle brachial index to classical risk factors improves the prediction of major cardiovascular events. The REGICOR study. *Atherosclerosis* 2015; 241: 357-363. 2015/06/15. DOI: 10.1016/j.atherosclerosis.2015.05.017.

123.	Authors/Task Force M, Piepoli MF, Hoes AW, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol* 2016; 23: NP1-NP96. 2016/06/30. DOI: 10.1177/2047487316653709.

124.	Simon A, Megnien JL and Levenson J. Detection of preclinical atherosclerosis may optimize the management of hypertension. *Am J Hypertens* 1997; 10: 813-824. 1997/07/01. DOI: 10.1016/s0895-7061(97)00118-0.

125.	Persson J, Formgren J, Israelsson B, et al. Ultrasound-determined intima-media thickness and atherosclerosis. Direct and indirect validation. *Arterioscler Thromb* 1994; 14: 261-264. 1994/02/01.

126.   Shemirani A-H, Zsóri KS, Jávor A, et al. Genetics in Peripheral Artery Disease. *Peripheral Arterial Disease - A Practical Approach*. 2018.

127.   Hiatt WR. Medical Treatment of Peripheral Arterial Disease and Claudication. *New England Journal of Medicine* 2001; 344: 1608-1621. DOI: 10.1056/nejm200105243442108.

128.   Hajibandeh S, Hajibandeh S, Shah S, et al. Prognostic significance of ankle brachial pressure index: A systematic review and meta-analysis. *Vascular* 2017; 25: 208-224. DOI: 10.1177/1708538116658392.

129.   Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg* 2019; 69: 3S-125S e140. 2019/06/05. DOI: 10.1016/j.jvs.2019.02.016.

130.   Aboyans V, Ricco JB, Bartelink MEL, et al. Editor's Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018; 55: 305-368. DOI: 10.1016/j.ejvs.2017.07.018.

131.   Quick CR and Cotton LT. The measured effect of stopping smoking on intermittent claudication. *The British journal of surgery* 1982; 69 Suppl: S24-26. 1982/06/01. DOI: 10.1002/bjs.1800691309.

132.   Jonason T and Bergström R. Cessation of smoking in patients with intermittent claudication. Effects on the risk of peripheral vascular complications, myocardial infarction and mortality. *Acta medica Scandinavica* 1987; 221: 253-260. 1987/01/01.

133.   Meade TW, Imeson J and Stirling Y. Effects of changes in smoking and other characteristics on clotting factors and the risk of ischaemic heart disease. *Lancet (London, England)* 1987; 2: 986-988. 1987/10/31. DOI: 10.1016/s0140-6736(87)92556-6.

134.   Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008: Cd000146. 2008/02/07. DOI: 10.1002/14651858.CD000146.pub3.

135.   García-Rodríguez O, Secades-Villa R, Flórez-Salamanca L, et al. Probability and predictors of relapse to smoking: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend* 2013; 132: 479-485. 2013/04/06. DOI: 10.1016/j.drugalcdep.2013.03.008.

136.   Barufaldi LA, Guerra RL, de Albuquerque RdCR, et al. Risk of smoking relapse with the use of electronic cigarettes: A systematic review with meta-analysis of longitudinal studies. *Tob Prev Cessat* 2021; 29: 29. DOI: 10.18332/tpc/132964.

137.   Berlin JA and Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. *Am J Epidemiol* 1990; 132: 612-628. 1990/10/01. DOI: 10.1093/oxfordjournals.aje.a115704.

138.   Stein RA, Rockman CB, Guo Y, et al. Association between physical activity and peripheral artery disease and carotid artery stenosis in a self-referred population of 3 million adults. *Arteriosclerosis, thrombosis, and vascular biology* 2015; 35: 206-212. 2014/11/02. DOI: 10.1161/atvbaha.114.304161.

139.   Peri-Okonny PA, Gosch K, Patel S, et al. Physical Activity in Patients with Symptomatic Peripheral Artery Disease: Insights from the PORTRAIT Registry. *Eur J Vasc Endovasc Surg* 2020; 60: 889-895. 2020/07/28. DOI: 10.1016/j.ejvs.2020.06.010.

140.   Milani RV and Lavie CJ. The role of exercise training in peripheral arterial disease. *Vasc Med* 2007; 12: 351-358. 2007/12/01. DOI: 10.1177/1358863x07083177.

141.   Hodges LD, Sandercock GR, Das SK, et al. Randomized controlled trial of supervised exercise to evaluate changes in cardiac function in patients with peripheral atherosclerotic disease. *Clin Physiol Funct Imaging* 2008; 28: 32-37. 2007/11/17. DOI: 10.1111/j.1475-097X.2007.00770.x.

142.   McDermott MM. Exercise Rehabilitation for Peripheral Artery Disease: A REVIEW. *J Cardiopulm Rehabil Prev* 2018; 38: 63-69. DOI: 10.1097/HCR.0000000000000343.

143.   Lauret GJ, Fakhry F, Fokkenrood HJ, et al. Modes of exercise training for intermittent claudication. *The Cochrane database of systematic reviews* 2014: Cd009638. 2014/07/06. DOI: 10.1002/14651858.CD009638.pub2.

144.   Heffron SP, Rockman CB, Adelman MA, et al. Greater Frequency of Fruit and Vegetable Consumption Is Associated With Lower Prevalence of Peripheral Artery Disease. *Arterioscler Thromb Vasc Biol* 2017; 37: 1234-1240. 2017/05/20. DOI: 10.1161/atvbaha.116.308474.

145.		Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk. *Circulation* 2014; 129: S76-S99. DOI: doi:10.1161/01.cir.0000437740.48606.d1.

146.		U.S. Department of Agriculture and U.S. Department of

Health and Human Services. Dietary Guidelines for Americans, 2020-2025, 9th Edition. 2020.

147.		Krauss RM, Eckel RH, Howard B, et al. AHA Dietary Guidelines: revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation* 2000; 102: 2284-2299. 2000/11/01. DOI: 10.1161/01.cir.102.18.2284.

148.		Organization WH. Obesity: preventing and managing the global epidemic. 2000.

149.		Poirier P, Giles TD, Bray GA, et al. Obesity and Cardiovascular Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2006; 26: 968-976. DOI: doi:10.1161/01.ATV.0000216787.85457.f3.

150.		Huang Y, Xu M, Xie L, et al. Obesity and peripheral arterial disease: A Mendelian Randomization analysis. *Atherosclerosis* 2016; 247: 218-224. 2016/03/08. DOI: 10.1016/j.atherosclerosis.2015.12.034.

151.		Heffron SP, Dwivedi A, Rockman CB, et al. Body mass index and peripheral artery disease. *Atherosclerosis* 2020; 292: 31-36. 2019/11/19. DOI: 10.1016/j.atherosclerosis.2019.10.017.

152.		Lavie CJ, Milani RV and Ventura HO. Obesity and Cardiovascular Disease: Risk Factor, Paradox, and Impact of Weight Loss. *Journal of the American College of Cardiology* 2009; 53: 1925-1932. DOI: https://doi.org/10.1016/j.jacc.2008.12.068.

153.		Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *European Journal of Preventive Cardiology* 2016; 23: 636-648. DOI: 10.1177/2047487315569401.

154.		Authors/Task Force M, Aboyans V, Ricco JB, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). *Eur J Vasc Endovasc Surg* 2017. DOI: 10.1016/j.ejvs.2017.07.018.

155.		Markel A. Statins and peripheral arterial disease. *Int Angiol* 2015; 34: 416-427. 2014/11/21.

156.		Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European heart journal* 2016; 37: 2315-2381. 2016/05/23. DOI: 10.1093/eurheartj/ehw106.

157.		Westin GG, Armstrong EJ, Bang H, et al. Association between statin medications and mortality, major adverse cardiovascular event, and amputation-free survival in patients with critical limb ischemia. *J Am Coll Cardiol* 2014; 63: 682-690. 2013/12/10. DOI: 10.1016/j.jacc.2013.09.073.

158.		Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *Circulation* 2014; 129: S1-S45. DOI: doi:10.1161/01.cir.0000437738.63853.7a.

159.		Murphy SA, Cannon CP, Blazing MA, et al. Reduction in Total Cardiovascular Events With Ezetimibe/Simvastatin Post-Acute Coronary Syndrome: The IMPROVE-IT Trial. *J Am Coll Cardiol* 2016; 67: 353-361. 2016/01/30. DOI: 10.1016/j.jacc.2015.10.077.

160.		Gencer B, Marston NA, Im K, et al. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. *Lancet* 2020; 396: 1637-1643. 2020/11/14. DOI: 10.1016/s0140-6736(20)32332-1.

161.		Bonaca MP, Nault P, Giugliano RP, et al. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease. *Circulation* 2018; 137: 338-350. DOI: doi:10.1161/CIRCULATIONAHA.117.032235.

162.		Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of

dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *European Heart Journal* 2019; 41: 111-188. DOI: 10.1093/eurheartj/ehz455.

163.   Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019; 73: 3168-3209. 2018/11/14. DOI: 10.1016/j.jacc.2018.11.002.

164.   Antithrombotic Trialists C. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ (Clinical research ed)* 2002; 324: 71-86. DOI: 10.1136/bmj.324.7329.71.

165.   Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 2018; 39: 763-816. DOI: 10.1093/eurheartj/ehx095.

166.   Bavry AA, Anderson RD, Gong Y, et al. Outcomes Among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the INternational VErapamil-SR/Trandolapril STudy. *Hypertension* 2010; 55: 48-53. 2009/12/10. DOI: 10.1161/hypertensionaha.109.142240.

167.   Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31: 1281-1357. 2013/07/03. DOI: 10.1097/01.hjh.0000431740.32696.cc.

168.   Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342: 145-153. 2000/01/20. DOI: 10.1056/nejm200001203420301.

169.   Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; 358: 1887-1898. 2008/04/02. DOI: 10.1056/NEJMoa0801369.

170.   Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359: 1577-1589. 2008/09/12. DOI: 10.1056/NEJMoa0806470.

171.   Peripheral Arterial Disease in People With Diabetes. *Diabetes Care* 2003; 26: 3333-3341. DOI: 10.2337/diacare.26.12.3333.

172.   Selvin E, Wattanakit K, Steffes MW, et al. HbA$_{1c}$ and Peripheral Arterial Disease in Diabetes. *Diabetes care* 2006; 29: 877. DOI: 10.2337/diacare.29.04.06.dc05-2018.

173.   Society for Vascular Surgery Lower Extremity Guidelines Writing G, Conte MS, Pomposelli FB, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg* 2015; 61: 2S-41S. DOI: 10.1016/j.jvs.2014.12.009.

174.   Alahdab F, Wang AT, Elraiyah TA, et al. A systematic review for the screening for peripheral arterial disease in asymptomatic patients. *J Vasc Surg* 2015; 61: 42S-53S. DOI: 10.1016/j.jvs.2014.12.008.

175.   Vaidya A, Joore MA, Ten Cate-Hoek AJ, et al. Screen or not to screen for peripheral arterial disease: guidance from a decision model. *BMC Public Health* 2014; 14: 89. DOI: 10.1186/1471-2458-14-89.

176.   Burns P, Gough S and Bradbury AW. Management of peripheral arterial disease in primary care. *BMJ (Clinical research ed)* 2003; 326: 584-588. DOI: 10.1136/bmj.326.7389.584.

177.   Rose GA, Blackburn H, Gillum R, et al. *Cardiovascular survey methods*. Geneva, Switzerland; WHO, 1982.

178.   Leng GC and Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol* 1992; 45: 1101-1109.

179.   Jain A, Liu K, Ferrucci L, et al. The Walking Impairment Questionnaire stair-climbing score predicts mortality in men and women with peripheral arterial disease. *J Vasc Surg* 2012; 55: 1662-1673 e1662. DOI: 10.1016/j.jvs.2011.12.010.

180.   Pickering TG, Hall JE, Appel LJ, et al. Recommendations for Blood Pressure Measurement in Humans and Experimental Animals. *Hypertension (Dallas, Tex : 1979)* 2005; 45: 142-161. DOI: doi:10.1161/01.HYP.0000150859.47929.8e.

181.   Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011; 11: 450. 2011/06/11. DOI: 10.1186/1471-2458-11-450.

182.   Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. *European journal of epidemiology* 2017; 32: 765-773. 2017/10/05. DOI: 10.1007/s10654-017-0316-1.

183.   Johansson LA and Westerling R. Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics. *Int J Epidemiol* 2000; 29: 495-502.

184.   Johansson LA and Westerling R. Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics. *International Journal of Epidemiology* 2000; 29: 495-502. DOI: 10.1093/intjepid/29.3.495.

185.   Wallerstedt SM, Wettermark B and Hoffmann M. The First Decade with the Swedish Prescribed Drug Register - A Systematic Review of the Output in the Scientific Literature. *Basic Clin Pharmacol Toxicol* 2016; 119: 464-469. 2016/04/27. DOI: 10.1111/bcpt.12613.

186.   Venermo M and Lees T. International Vascunet Validation of the Swedvasc Registry. *European Journal of Vascular and Endovascular Surgery* 2015; 50: 802-808. DOI: https://doi.org/10.1016/j.ejvs.2015.07.021.

187.   Ng R, Kornas K, Sutradhar R, et al. The current application of the Royston-Parmar model for prognostic modeling in health research: a scoping review. *Diagnostic and Prognostic Research* 2018; 2: 4. DOI: 10.1186/s41512-018-0026-5.

188.   Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; 338: b2393. DOI: 10.1136/bmj.b2393.

189.   World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310: 2191-2194. DOI: 10.1001/jama.2013.281053.

190.   Björk J, Berglund A, Härkönen J, et al. Practical and methodological issues in register-based research. *Scandinavian Journal of Public Health* 2017; 45: 3-4. DOI: 10.1177/1403494817709727.

191.   Thygesen LC and Ersbøll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. *Eur J Epidemiol* 2014; 29: 551-558. 2014/01/11. DOI: 10.1007/s10654-013-9873-0.

192.   Hannah L Brooke MJH, Ola Olén, Mats Talbäck, Maria Feychting, Anita Berglund, Jonas F Ludvigsson, Rickard Ljung. Enhancing evidence based medicine: Twelve tips for conducting register-based research. *MedEdPublish* 2016. Medical Education (General), Research in Medical Education, Teachers/Trainers (including Faculty Development).

193.   Vart P, Coresh J, Kwak L, et al. Socioeconomic Status and Incidence of Hospitalization With Lower-Extremity Peripheral Artery Disease: Atherosclerosis Risk in Communities Study. *J Am Heart Assoc* 2017; 6 2017/09/02. DOI: 10.1161/jaha.116.004995.

194.   Creager MA, Matsushita K, Arya S, et al. Reducing Nontraumatic Lower-Extremity Amputations by 20% by 2030: Time to Get to Our Feet. *Circulation*; 0: CIR.0000000000000967. DOI: doi:10.1161/CIR.0000000000000967.

195.   Song P, Rudan D, Zhu Y, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *The Lancet Global health* 2019; 7: e1020-e1030. 2019/07/16. DOI: 10.1016/s2214-109x(19)30255-4.

196.   Sweden S. Life expectancy 2020.

197.   Björck L, Rosengren A, Bennett K, et al. Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. *European Heart Journal* 2009; 30: 1046-1056. DOI: 10.1093/eurheartj/ehn554.

198.	Fowkes FG, Housley E, Cawood EH, et al. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *International journal of epidemiology* 1991; 20: 384-392. 1991/06/01. DOI: 10.1093/ije/20.2.384.

199.	Meijer WT, Hoes AW, Rutgers D, et al. Peripheral arterial disease in the elderly: The Rotterdam Study. *Arteriosclerosis, thrombosis, and vascular biology* 1998; 18: 185-192. 1998/03/04. DOI: 10.1161/01.atv.18.2.185.

200.	Fabsitz RR, Sidawy AN, Go O, et al. Prevalence of peripheral arterial disease and associated risk factors in American Indians: the Strong Heart Study. *American journal of epidemiology* 1999; 149: 330-338. 1999/02/20. DOI: 10.1093/oxfordjournals.aje.a009817.

201.	Vogt MT, Cauley JA, Kuller LH, et al. Prevalence and Correlates of Lower Extremity Arterial Disease in Elderly Women. *American journal of epidemiology* 1993; 137: 559-568. DOI: 10.1093/oxfordjournals.aje.a116709.

202.	Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: Objectives and Design. *American journal of epidemiology* 2002; 156: 871-881. DOI: 10.1093/aje/kwf113.

203.	Diehm C, Schuster A, Allenberg JR, et al. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. *Atherosclerosis* 2004; 172: 95-105. 2004/01/08. DOI: 10.1016/s0021-9150(03)00204-1.

204.	Criqui MH, Vargas V, Denenberg JO, et al. Ethnicity and peripheral arterial disease: the San Diego Population Study. *Circulation* 2005; 112: 2703-2707. 2005/10/26. DOI: 10.1161/circulationaha.105.546507.

205.	Fisher CM, Burnett A, Makeham V, et al. Variation in measurement of ankle-brachial pressure index in routine clinical practice. *Journal of Vascular Surgery* 1996; 24: 871-875. DOI: https://doi.org/10.1016/S0741-5214(96)70025-3.

206.	Gornik HL, Garcia B, Wolski K, et al. Validation of a method for determination of the ankle-brachial index in the seated position. *J Vasc Surg* 2008; 48: 1204-1210. 2008/10/03. DOI: 10.1016/j.jvs.2008.06.052.

207.	Smith FB, Lee AJ, Price JF, et al. Changes in ankle brachial index in symptomatic and asymptomatic subjects in the general population. *Journal of Vascular Surgery* 2003; 38: 1323-1330. DOI: https://doi.org/10.1016/S0741-5214(03)01021-8.

208.	Kapoor R, Ayers C, Visotcky A, et al. Association of sex and height with a lower ankle brachial index in the general population. *Vascular medicine (London, England)* 2018; 23: 534-540. 2018/06/06. DOI: 10.1177/1358863x18774845.

209.	Ahn J-H and Kong M. The Relationship among Pulse Wave Velocity, Ankle-Brachial Pressure Index and Heart Rate Variability in Adult Males. *Korean J Fam Med* 2011; 32: 406-411. 2011/11/30. DOI: 10.4082/kjfm.2011.32.7.406.

210.	Safar ME, Protogerou AD and Blacher J. Statins, Central Blood Pressure, and Blood Pressure Amplification. *Circulation* 2009; 119: 9-12. DOI: doi:10.1161/CIRCULATIONAHA.108.824532.

211.	Yeboah K, Puplampu P, Yorke E, et al. Body composition and ankle-brachial index in Ghanaians with asymptomatic peripheral arterial disease in a tertiary hospital. *BMC Obesity* 2016; 3: 27. DOI: 10.1186/s40608-016-0107-3.

212.	Velescu A, Clara A, Marti R, et al. Abnormally High Ankle-Brachial Index is Associated with All-cause and Cardiovascular Mortality: The REGICOR Study. *Eur J Vasc Endovasc Surg* 2017; 54: 370-377. 2017/07/30. DOI: 10.1016/j.ejvs.2017.06.002.

213.	Hendriks EJ, Westerink J, de Jong PA, et al. Association of High Ankle Brachial Index With Incident Cardiovascular Disease and Mortality in a High-Risk Population. *Arteriosclerosis, thrombosis, and vascular biology* 2016; 36: 412-417. 2015/12/31. DOI: 10.1161/atvbaha.115.306657.

214.	Wattanakit K, Folsom AR, Duprez DA, et al. Clinical significance of a high ankle-brachial index: insights from the Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis* 2007; 190: 459-464. 2006/04/01. DOI: 10.1016/j.atherosclerosis.2006.02.039.

215.	Golledge J, Moxon JV, Rowbotham S, et al. High ankle brachial index predicts high risk of cardiovascular events amongst people with peripheral artery disease. *PloS one* 2020; 15: e0242228. 2020/11/13. DOI: 10.1371/journal.pone.0242228.

216.	Wohlfahrt P, Palouš D, Ingrischová M, et al. A high ankle-brachial index is associated with increased aortic pulse wave velocity: the Czech post-MONICA study. *European Journal of Cardiovascular Prevention & Rehabilitation* 2011; 18: 790-796. DOI: 10.1177/1741826711398840.

217.	Dachun X, Jue L, Liling Z, et al. Sensitivity and specificity of the ankle—brachial index to diagnose peripheral artery disease: a structured review. *Vascular Medicine* 2010; 15: 361-369. DOI: 10.1177/1358863X10378376.

218.	Lin X, Xu Y, Pan X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. *Scientific Reports* 2020; 10: 14790. DOI: 10.1038/s41598-020-71908-9.

219.	Organisation WH. Health topics / Diabetes 2021.

220.	Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes research and clinical practice* 2019; 157: 107843. 2019/09/14. DOI: 10.1016/j.diabres.2019.107843.

221.	Tat V and Forest CP. The role of SGLT2 inhibitors in managing type 2 diabetes. *JAAPA : official journal of the American Academy of Physician Assistants* 2018; 31: 35-40. 2018/05/31. DOI: 10.1097/01.Jaa.0000533660.86287.04.

222.	Chase-Vilchez AZ, Chan IHY, Peters SAE, et al. Diabetes as a risk factor for incident peripheral arterial disease in women compared to men: a systematic review and meta-analysis. *Cardiovascular Diabetology* 2020; 19: 151. DOI: 10.1186/s12933-020-01130-4.

223.	Mills KT, Stefanescu A and He J. The global epidemiology of hypertension. *Nature Reviews Nephrology* 2020; 16: 223-237. DOI: 10.1038/s41581-019-0244-2.

224.	Alexander RW. Theodore Cooper Memorial Lecture. Hypertension and the pathogenesis of atherosclerosis. Oxidative stress and the mediation of arterial inflammatory response: a new perspective. *Hypertension (Dallas, Tex : 1979)* 1995; 25: 155-161. 1995/02/01. DOI: 10.1161/01.hyp.25.2.155.

225.	Allison MA, Criqui MH, McClelland RL, et al. The Effect of Novel Cardiovascular Risk Factors on the Ethnic-Specific Odds for Peripheral Arterial Disease in the Multi-Ethnic Study of Atherosclerosis (MESA). *Journal of the American College of Cardiology* 2006; 48: 1190-1197. DOI: https://doi.org/10.1016/j.jacc.2006.05.049.

226.	Murabito JM, Evans JC, Nieto K, et al. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. *American heart journal* 2002; 143: 961-965. 2002/06/21. DOI: 10.1067/mhj.2002.122871.

227.	WHO. Global Health Observatory (GHO) data - Mean cholesterol. 2021.

228.	Taddei C, Zhou B, Bixby H, et al. Repositioning of the global epicentre of non-optimal cholesterol. *Nature* 2020; 582: 73-77. DOI: 10.1038/s41586-020-2338-1.

229.	Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet (London, England)* 2016; 387: 1377-1396. 2016/04/27. DOI: 10.1016/s0140-6736(16)30054-x.

230.	Lovren F, Teoh H and Verma S. Obesity and atherosclerosis: mechanistic insights. *The Canadian journal of cardiology* 2015; 31: 177-183. 2015/02/11. DOI: 10.1016/j.cjca.2014.11.031.

231.	Bilano V, Gilmour S, Moffiet T, et al. Global trends and projections for tobacco use, 1990-2025: an analysis of smoking indicators from the WHO Comprehensive Information Systems for Tobacco Control. *Lancet (London, England)* 2015; 385: 966-976. 2015/03/19. DOI: 10.1016/s0140-6736(15)60264-1.

232.	Hobbs SD and Bradbury AW. Smoking Cessation Strategies in Patients with Peripheral Arterial Disease: An Evidence-based Approach. *European Journal of Vascular and Endovascular Surgery* 2003; 26: 341-347. DOI: https://doi.org/10.1016/S1078-5884(03)00356-3.

233.	Fiotti N, Altamura N, Cappelli C, et al. Long Term Prognosis in Patients with Peripheral Arterial Disease Treated with Antiplatelet Agents. *European Journal of Vascular and Endovascular Surgery* 2003; 26: 374-380. DOI: https://doi.org/10.1016/S1078-5884(03)00318-6.

234.	Yannoutsos A, Fontaine M, Galloula A, et al. Peripheral arterial disease and systematic detection of circulating tumor cells: rationale and design of the DETECTOR prospective cohort study. *BMC Cardiovascular Disorders* 2019; 19: 212. DOI: 10.1186/s12872-019-1193-1.

235.	van Kruijsdijk RC, van der Graaf Y, Peeters PH, et al. Cancer risk in patients with manifest vascular disease: effects of smoking, obesity, and metabolic syndrome. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2013; 22: 1267-1277. 2013/05/17. DOI: 10.1158/1055-9965.Epi-13-0090.

236.	Taute B-M, Thommes S, Taute R, et al. The Possible Risk of Cancer in Claudicants. *Angiology* 2011; 62: 579-584. DOI: 10.1177/0003319711400308.

237.	McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. *Jama* 2004; 292: 453-461. 2004/07/29. DOI: 10.1001/jama.292.4.453.

238.	Mohler ER, 3rd, Bundens W, Denenberg J, et al. Progression of asymptomatic peripheral artery disease over 1 year. *Vasc Med* 2012; 17: 10-16. 2012/03/01. DOI: 10.1177/1358863x11431106.

239.	Behroozian AA and Beckman JA. Asymptomatic peripheral artery disease: Silent but deadly. *Progress in Cardiovascular Diseases* 2021. DOI: https://doi.org/10.1016/j.pcad.2021.02.009.

240.	McDermott MM, Guralnik JM, Ferrucci L, et al. Asymptomatic peripheral arterial disease is associated with more adverse lower extremity characteristics than intermittent claudication. *Circulation* 2008; 117: 2484-2491.

241.	Mahoney EM, Wang K, Keo HH, et al. Vascular Hospitalization Rates and Costs in Patients With Peripheral Artery Disease in the United States. *Circulation: Cardiovascular Quality and Outcomes* 2010; 3: 642-651. DOI: doi:10.1161/CIRCOUTCOMES.109.930735.

242.	Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet (London, England)* 2016; 388: 2532-2561. 2016/09/13. DOI: 10.1016/s0140-6736(16)31357-5.

243.	Stancu C and Sima A. Statins: mechanism of action and effects. *Journal of cellular and molecular medicine* 2001; 5: 378-387. 2002/06/18. DOI: 10.1111/j.1582-4934.2001.tb00172.x.

244.	Ramkumar S, Raghunath A and Raghunath S. Statin Therapy: Review of Safety and Potential Side Effects. *Acta Cardiol Sin* 2016; 32: 631-639. DOI: 10.6515/acs20160611a.

245.	Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *The New England journal of medicine* 2015; 372: 2387-2397. 2015/06/04. DOI: 10.1056/NEJMoa1410489.

246.	Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ (Clinical research ed)* 2002; 324: 71-86. 2002/01/12. DOI: 10.1136/bmj.324.7329.71.

247.	A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet (London, England)* 1996; 348: 1329-1339. 1996/11/16. DOI: 10.1016/s0140-6736(96)09457-3.

248.	Steffel J, Eikelboom JW, Anand SS, et al. The COMPASS Trial. *Circulation* 2020; 142: 40-48. DOI: doi:10.1161/CIRCULATIONAHA.120.046048.

249.	Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. *The New England journal of medicine* 2020; 382: 1994-2004. 2020/03/30. DOI: 10.1056/NEJMoa2000052.

250.	Armstrong EJ, Chen DC, Singh GD, et al. Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use is associated with reduced major adverse cardiovascular events among patients with critical limb ischemia. *Vascular medicine (London, England)* 2015; 20: 237-244. 2015/04/04. DOI: 10.1177/1358863x15574321.

251.	Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *The New England journal of medicine* 2008; 358: 1547-1559. 2008/04/02. DOI: 10.1056/NEJMoa0801317.

252.	Sleight P. The HOPE Study (Heart Outcomes Prevention Evaluation). *Journal of the renin-angiotensin-aldosterone system : JRAAS* 2000; 1: 18-20. 2002/04/23. DOI: 10.3317/jraas.2000.002.

253.	Berger JS, Krantz MJ, Kittelson JM, et al. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *Jama* 2009; 301: 1909-1919. 2009/05/14. DOI: 10.1001/jama.2009.623.

254.	Catalano M, Born G and Peto R. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. *Journal of internal medicine* 2007; 261: 276-284. 2007/02/20. DOI: 10.1111/j.1365-2796.2006.01763.x.

255.	Fowkes FG, Price JF, Stewart MC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA* 2010; 303: 841-848. 2010/03/04. DOI: 10.1001/jama.2010.221.

256.	Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ (Clinical research ed)* 2008; 337: a1840. DOI: 10.1136/bmj.a1840.

257.	Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions. *J Vasc Surg* 2007; 45: 645-654; discussion 653-644. 2007/04/03. DOI: 10.1016/j.jvs.2006.12.054.

258.	Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *The New England journal of medicine* 2008; 359: 2195-2207. 2008/11/11. DOI: 10.1056/NEJMoa0807646.

259.	Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *The New England journal of medicine* 1998; 339: 1349-1357. 1998/12/05. DOI: 10.1056/nejm199811053391902.

260.	Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *The New England journal of medicine* 2017; 376: 1713-1722. 2017/03/18. DOI: 10.1056/NEJMoa1615664.

261.	Caro J, Migliaccio-Walle K, Ishak KJ, et al. The morbidity and mortality following a diagnosis of peripheral arterial disease: long-term follow-up of a large database. *BMC Cardiovasc Disord* 2005; 5: 14-14. DOI: 10.1186/1471-2261-5-14.

262.	Sigvant B, Kragsterman B, Falkenberg M, et al. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. *J Vasc Surg* 2016; 64: 1009-1017 e1003. DOI: 10.1016/j.jvs.2016.03.429.

263.	Hirsch AT and Hiatt WR. PAD awareness, risk, and treatment: new resources for survival--the USA PARTNERS program. *Vasc Med* 2001; 6: 9-12. 2002/01/16. DOI: 10.1177/1358836X0100600i103.

264.	Søgaard M, Nielsen PB, Skjøth F, et al. Temporal Changes in Secondary Prevention and Cardiovascular Outcomes After Revascularization for Peripheral Arterial Disease in Denmark: A Nationwide Cohort Study. *Circulation* 2021; 143: 907-920. 2020/12/11. DOI: 10.1161/circulationaha.120.047994.

265.	Baviera M, Bertelè V, Avanzini F, et al. Peripheral arterial disease: Changes in clinical outcomes and therapeutic strategies in two cohorts, from 2002 to 2008 and from 2008 to 2014. A population-based study. *European Journal of Preventive Cardiology* 2020; 25: 1735-1743. DOI: 10.1177/2047487318770299.

266.	Berger JS and Ladapo JA. Underuse of Prevention and Lifestyle Counseling in Patients With Peripheral Artery Disease. *J Am Coll Cardiol* 2017; 69: 2293-2300. 2017/05/06. DOI: 10.1016/j.jacc.2017.02.064.

267.	Jones WS, Mi X, Qualls LG, et al. Significant variation in P2Y12 inhibitor use after peripheral vascular intervention in Medicare beneficiaries. *American Heart Journal* 2016; 179: 10-18. DOI: https://doi.org/10.1016/j.ahj.2016.06.002.

268.   Subherwal S, Patel MR, Kober L, et al. Missed Opportunities. *Circulation* 2012; 126: 1345-1354. DOI: doi:10.1161/CIRCULATIONAHA.112.108787.

269.   Gasse C, Jacobsen J, Larsen AC, et al. Secondary medical prevention among Danish patients hospitalised with either peripheral arterial disease or myocardial infarction. *Eur J Vasc Endovasc Surg* 2008; 35: 51-58. 2007/10/10. DOI: 10.1016/j.ejvs.2007.08.008.

270.   Watson K, Watson BD and Pater KS. Peripheral arterial disease: a review of disease awareness and management. *Am J Geriatr Pharmacother* 2006; 4: 365-379. 2007/02/14. DOI: 10.1016/j.amjopharm.2006.12.006.

271.   Gunnarsson T, Gottsäter A, Bergman S, et al. Eight-year outcome after invasive treatment of infrainguinal intermittent claudication: A population-based analysis from the Swedish vascular register (Swedvasc). *SAGE Open Med* 2020; 8: 2050312120926782. 2020/06/18. DOI: 10.1177/2050312120926782.

272.   Criqui MH, Denenberg JO, Langer RD, et al. The epidemiology of peripheral arterial disease: importance of identifying the population at risk. *Vasc Med* 1997; 2: 221-226. DOI: 10.1177/1358863X9700200310.

273.   Barquera S, Pedroza-Tobías A, Medina C, et al. Global Overview of the Epidemiology of Atherosclerotic Cardiovascular Disease. *Arch Med Res* 2015; 46: 328-338. 2015/07/03. DOI: 10.1016/j.arcmed.2015.06.006.

274.   Rosengren A, Smyth A, Rangarajan S, et al. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study. *Lancet Glob Health* 2019; 7: e748-e760. 2019/04/28. DOI: 10.1016/S2214-109X(19)30045-2.

275.   Dagli RJ and Sharma A. Polypharmacy: a global risk factor for elderly people. *J Int Oral Health* 2014; 6: i-ii.

276.   Organization WH. 'BEST BUYS' AND OTHER RECOMMENDED INTERVENTIONS

FOR THE PREVENTION AND CONTROL OF NONCOMMUNICABLE DISEASES. 2017; UPDATED (2017) APPENDIX 3 OF THE GLOBAL ACTION PLAN

FOR THE PREVENTION AND CONTROL OF NONCOMMUNICABLE DISEASES 2013-2020.

277.   Jukema JW, Szarek M, Zijlstra LE, et al. Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndrome: ODYSSEY OUTCOMES Trial. *J Am Coll Cardiol* 2019; 74: 1167-1176. 2019/03/23. DOI: 10.1016/j.jacc.2019.03.013.

278.   Carbone S and Dixon DL. The CANVAS Program: implications of canagliflozin on reducing cardiovascular risk in patients with type 2 diabetes mellitus. *Cardiovascular Diabetology* 2019; 18: 64. DOI: 10.1186/s12933-019-0869-2.

279.   Chatterjee S, Bandyopadhyay D, Ghosh RK, et al. SGLT-2 Inhibitors and Peripheral Artery Disease: A Statistical Hoax or Reality? *Current problems in cardiology* 2019; 44: 207-222. 2018/09/10. DOI: 10.1016/j.cpcardiol.2018.06.004.

280.   Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *New England Journal of Medicine* 2017; 377: 644-657. DOI: 10.1056/NEJMoa1611925.

281.   Joseph P, Pais P, Dans AL, et al. The International Polycap Study-3 (TIPS-3): Design, baseline characteristics and challenges in conduct. *Am Heart J* 2018; 206: 72-79. 2018/10/21. DOI: 10.1016/j.ahj.2018.07.012.

282.   Roshandel G, Khoshnia M, Poustchi H, et al. Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial. *Lancet* 2019; 394: 672-683. 2019/08/27. DOI: 10.1016/s0140-6736(19)31791-x.

283.   Björck L, Rosengren A, Bennett K, et al. Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. *Eur Heart J* 2009; 30: 1046-1056. 2009/01/15. DOI: 10.1093/eurheartj/ehn554.

284.   Haile S, Linné A, Johansson UB, et al. Follow-up after surgical treatment for intermittent claudication (FASTIC): a study protocol for a multicentre randomised controlled clinical trial. *BMC nursing* 2020; 19: 45. 2020/06/11. DOI: 10.1186/s12912-020-00437-7.