TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Peripheral Pressure Measurements: Association with Cardiovascular Mortality and Intracranial Aneurysms

Essi Kangas

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1903 | MEDICA – ODONTOLOGICA | TURKU 2025

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

PERIPHERAL PRESSURE MEASUREMENTS: ASSOCIATION WITH CARDIOVASCULAR MORTALITY AND INTRACRANIAL ANEURYSMS

Essi Kangas

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1903 | MEDICA – ODONTOLOGICA | TURKU 2025

University of Turku

Faculty of Medicine
Department of Clinical Medicine
Surgery
Doctoral Programme in Clinical Research (DPCR)

Supervised by

Professor Harri Hakovirta, MD
VARHA, Sydänkeskus
Turku University Hospital
Turku, Finland

PhD Dan Laukka, MD
Clinical Neurosciences
Turku University Hospital
Turku, Finland

Docent Petra Korpisalo, MD
Heart Center
Kuopio University Hospital
Kuopio, Finland

Reviewed by

Docent Velipekka Suominen, MD
Center for Vascular surgery and
Interventional radiology
Tampere University Hospital
Tampere, Finland

Docent Jukka Huttunen, MD
Neurosurgery of KUH NeuroCenter
Kuopio University Hospital
Kuopio, Finland

Opponent

Docent Ilkka Uurto, MD
Center for Vascular surgery and
Interventional radiology
Tampere University Hospital
Tampere, Finland

ISBN 978-952-02-0319-1 (PRINT)
ISBN 978-952-02-0320-7 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland

To Alvin and Leia

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Clinical Medicine
Surgery
ESSI KANGAS: Peripheral Pressure Measurements: Association with Cardiovascular Mortality and Intracranial Aneurysms
Doctoral Dissertation, 150 pp.
Doctoral Programme in Clinical Research
September 2025

ABSTRACT

Peripheral artery disease (PAD) is associated with increased overall and cardiovascular (CV) mortality. A significant proportion of patients with PAD also have atherosclerotic changes in other vascular territories, such as the coronary and cerebral arteries. Peripheral pressure measurements—ankle-brachial index (ABI), toe-brachial index (TBI) and toe pressure—are widely used to assess limb circulation and can provide valuable insights into overall CV risk. The normal ABI range is defined as 0.9–1.4. However, prior research suggests that mortality increases even among individuals with ABI values near the lower limit of normal (0.9–1.0), and that an elevated ABI (>1.4) is likewise associated with higher mortality.

Intracranial aneurysms (IAs) occur in approximately 3% of the adult population. They are typically asymptomatic until rupture, which carries a high risk of death and long-term disability. PAD and IA share several risk factors and pathogenic similarities, but the role of atherosclerosis in IA formation remains unclear.

The aim of this dissertation was to examine the relationship of normal and high ABI values with overall and CV mortality, and to investigate the association of ABI and TBI with the prevalence of IAs. The study cohort consisted of 2,751 patients who underwent lower limb pressure measurements at the vascular laboratory of Turku University Hospital between 2011 and 2013. Data were collected retrospectively after the follow-up period.

The results showed that a low-normal ABI (0.9–1.0) was associated with increased overall and CV mortality compared with ABI values between 1.0 and 1.29, even when both lower limbs had values within the range of 0.8–1.4. In the high ABI group (>1.3), ankle artery incompressibility was most strongly associated with increased mortality and CV morbidity. Another key finding was the strong association between low ABI and TBI values and the prevalence of IAs: a low ABI (<0.9) was associated with a ninefold higher prevalence of IAs, and a low TBI (<0.5) with a fourfold increase, in comparison with normal ABI and TBI values.

KEYWORDS: Peripheral artery disease, ankle-brachial index, toe-brachial index, cardiovascular mortality, intracranial aneurysm

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Kirurgia
ESSI KANGAS: Alaraajojen painemittausten yhteys kardiovaskulaarikuolleisuuteen ja aivovaltimoaneurysmien esiintyvyyteen
Väitöskirja, 150 s.
Turun kliininen tohtoriohjelma
Syyskuu 2025

TIIVISTELMÄ

Alaraajojen tukkiva valtimotauti on yhteydessä kohonneeseen kokonais- ja kardiovaskulaarikuolleisuuteen. Merkittävällä osalla potilaista todetaan samanaikaisesti valtimokovettumatautimuutoksia myös muissa valtimorakenteissa, kuten sepelvaltimoissa tai aivovaltimoissa. Nilkka-olkavarsipainesuhdetta (ABI), varvas-olkavarsipainesuhdetta (TBI) ja varvaspaineita käytetään alaraajojen verenkierron arvioinnissa ja niiden avulla pystytään myös määrittää potilaan yleistä valtimotautiriskiä. ABI:n normaalialueeksi on määritelty 0.9–1.4 alaraajojen verenkiertoa arvioitaessa. Jo normaalin alarajalla oleva ABI (0.9–1.0) on havaittu liittyvän suurentuneeseen kokonais- ja kardiovaskulaarikuolleisuuteen, ja myös kohonnut ABI (>1.4) on todettu olevan yhteydessä heikentyneeseen ennusteeseen.

Aivovaltimoaneurysmia esiintyy noin kolmella prosentilla aikuisväestöstä. Aneurysma on useimmiten oireeton, mutta puhjetessaan voi aiheuttaa merkittävää kuolleisuutta ja pysyvää toimintakyvyn laskua. Valtimokovettumataudin ja aivovaltimoaneurysmien välillä on yhteneväisyyksiä niin riskitekijöissä kuin myös syntymekanismeissa, mutta niiden välinen yhteys on edelleen tuntematon.

Tutkimusten tavoitteena oli selvittää normaalin ja korkean ABI:n yhteys kokonais- ja kardiovaskulaarikuolleisuuteen sekä arvioida ABI:n ja TBI:n yhteyttä aivovaltimoaneurysmien esiintyvyyteen. Tutkimusaineisto käsitti 2751 potilasta, jotka kävivät vuosien 2011–2013 aikana alaraajojen painemittauksissa Turun yliopistollisen keskussairaalan verisuonilaboratoriossa. Tutkimusaineisto kerättiin retrospektiivisesti seurantajakson päätyttyä.

Tulokset osoittivat, että jo normaalin alarajalla oleva ABI (0.9–1.0) oli yhteydessä suurentuneeseen kokonais- ja kardiovaskulaarikuolleisuuteen myös silloin, kun arvot olivat lähes normaalialueella molemmista alaraajoista mitattuna (0.8-1.4). Potilailla, joiden ABI oli yli 1.3, heikoin ennuste todettiin niillä, joilla, nilkkavaltimot olivat kokoonpuristumattomat. Lisäksi matala ABI (<0.9) lisäsi aivovaltimoaneurysmien esiintyvyyttä yhdeksänkertaisesti ja matala TBI (<0.5) nelinkertaisesti normaaliarvoihin verrattuna.

AVAINSANAT: Alaraajojen tukkiva valtimotauti, nilkka-olkavarsipainesuhde, varvas-olkavarsipainesuhde, kardiovaskulaarikuolleisuus, aivovaltimoaneurysma

Table of Contents

Abbreviations

ABI	Ankle-brachial index
ASA	Acetylsalicylic acid
ADPKD	Autosomal dominant polycystic kidney disease
aSAH	Aneurysmatic subarachnoid hemorrhage
AR	Aspect ratio
BMI	Body mass index
CAD	Coronary artery disease
CeVD	Cerebrovascular disease
CKD	Chronic kidney disease
CLTI	Chronic limb-threatening ischemia
CV	Cardiovascular
CVD	Cardiovascular disease
EC	Endothelial cell
ECM	Extracellular matrix
eGFR	Estimated glomerular filtration rate
HDL	High-density lipoprotein
HICs	High-income countries
HR	Hazard Ratio
IA	Intracranial aneurysm
IC	Intermitted claudication
ICAM-1	Intercellular adhesion molecule-1
IEL	Internal elastic lamina
IL-6	Interleukin-6
LDL	Low-density lipoprotein
LMICs	Low- and middle-income countries
MAC	Medial arterial calcification
MACE	Major adverse cardiovascular events
MALE	Major adverse limb events
MetS	Metabolic syndrome
MGP	Matrix Gla protein
MMP	Matrix metalloproteinases

MVs	Matrix vesicles
NF- κB	Nuclear factor Kappa-beta
NHANES	National Health and Nutrition Examination Survey
NO	Nitric oxide
OR	Odds ratio
oxLDL	Oxidized LDL
PAD	Peripheral artery disease
REACH	Reduction of Atherothrombosis for Continued Health (registry)
RR	Risk ratio
SAH	Subarachnoid hemorrhage
SBP	Systolic blood pressure
TBI	Toe-brachial index
TNF-α	Tumor necrosis factor-alpha
TP	Toe pressure
VCAM-1	Vascular cell adhesion molecule-1
VSMCs	Vascular smooth muscle cells
WSS	Wall shear stress

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Peltonen E, Laivuori M, Vakhitov D, Korhonen P, Venermo M, Hakovirta H. The Cardiovascular-Mortality-Based Estimate for Normal Range of the Ankle-Brachial Index (ABI). J Cardiovasc Dev Dis. 2022; 9:147.

II Laivuori M, Peltonen E, Venermo M, Hakovirta H. Incompressible ankle arteries predict increased morbidity and mortality in patients with an elevated ankle brachial index. Vascular. 2024; 32:110–117.

III Laukka D, Kangas E, Kuusela A, Hirvonen J, Rissanen T, Rahi M, Kivelev J, Rantasalo V, Venermo M, Rinne J, Hakovirta H. Low and Borderline Ankle-Brachial Index Is Associated With Intracranial Aneurysms: A Retrospective Cohort Study. Neurosurgery. 2024; 94:1282–90.

IV Kangas E, Rantasalo V, Korpisalo P, Kuusela A, Hakovirta E, Korhonen P, Rahi M, Kivelev J, Rinne J, Venermo M, Hirvonen J, Hakovirta H, Laukka D. A High Prevalence of Saccular Intracranial Aneurysms Associated with Low Toe-Brachial Index. Manuscript.

1 Introduction

Cardiovascular diseases (CVD) remain a leading cause of morbidity and mortality worldwide, with their impact extending beyond coronary and cerebrovascular territories.[1] Among these, peripheral artery disease (PAD) is a prevalent yet frequently underdiagnosed condition, with an estimated global prevalence of 237 million individuals in 2015.[2] PAD is a vascular disorder characterized by the narrowing or occlusion of arteries, predominantly in the lower extremities, primarily due to atherosclerotic changes. Patients with PAD face a significantly higher risk of experiencing myocardial infarction and stroke and their long-term prognosis is notably poorer, with a mortality rate up to six times higher over a 10-year period compared to individuals without PAD.[3] Consequently, the identification of PAD and the management of its risk factors are of paramount importance in reducing the burden of CVDs.

A widely used, non-invasive diagnostic method for assessing PAD is the ankle-brachial index (ABI), which is a simple ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the brachial artery. A low ABI is indicative of arterial stenosis or occlusion in the lower extremities. Despite its utility, the ABI may be less accurate in individuals with non-compressible arteries, which can occur in populations with diabetes or chronic kidney disease (CKD).[4] In such cases, the toe-brachial index (TBI) and toe pressure (TP) offer an alternative diagnostic measure, particularly useful for detecting PAD in individuals with incompressible ankle arteries.[5]

The clinical relevance of pressure measurements extends beyond their diagnostic capacity for PAD. Both the ABI and TBI have been shown to correlate with mortality and morbidity across various populations.[6,7] As such, these indices serve as valuable prognostic tests for clinicians, providing insight into the overall cardiovascular (CV) health of patients and allowing for the identification of individuals at heightened risk.

An intracranial aneurysm (IA) is an abnormal bulging in the wall of a cerebral artery. Upon rupture, it can lead to a catastrophic event, a subarachnoid hemorrhage (SAH), with high morbidity and mortality rates. Although the exact mechanisms remain unclear, shared risk factors, such as hypertension and smoking, may

contribute to the co-occurrence of PAD and IAs.[8] The hypothesis that the ABI and TBI, which reflect systemic atherosclerosis, could be associated with IA development is a novel area of investigation.

2 Review of the Literature

2.1 Peripheral artery disease

2.1.1 Epidemiology

PAD is a common manifestation of systemic atherosclerosis, characterized by the narrowing or occlusion of peripheral arteries, primarily in the lower extremities. PAD affects over 200 million individuals worldwide, with the prevalence steadily increasing over recent decades. Epidemiological data indicate that the global prevalence of PAD rose by 17% between 2010 and 2015.[2] The incidence and prevalence of PAD are strongly correlated with advancing age, and as life expectancy continues to rise, shifting global demographics towards an older population, the prevalence of PAD is expected to increase in the future. This trend underscores the growing public health burden of PAD, particularly in aging populations.[9] Patients with PAD experience significantly higher healthcare costs compared to those without the condition, primarily due to increased hospitalizations, the need for surgical interventions, management of comorbidities, and long-term care for complications such as chronic limb-threatening ischemia (CLTI) and amputation.[10,11] PAD is relatively uncommon in individuals under the age of 50. However, its prevalence increases progressively with age, with approximately 20% of individuals aged 80 years having PAD.[2]

Epidemiological data indicate substantial geographic variations in PAD prevalence, influenced by both environmental and genetic factors, as well as differences in healthcare access and socioeconomic status. Notwithstanding, high-income countries (HICs) exhibit a higher absolute prevalence of PAD, but the majority of global cases (72.91%) are concentrated in low- and middle-income countries (LMICs). Between 2010 and 2015, the relative increase in PAD prevalence was substantially greater in LMICs compared to HICs (22.6% vs. 4.5%), a trend driven by rapid urbanization, rising prevalence of risk factors such as diabetes and hypertension, and obesity. The limited healthcare infrastructure in LMICs exacerbates the disease burden in these populations.[2,9,12]

In HICs, PAD prevalence is observed to be higher among women until the age of 75 years, after which it becomes more prevalent among men. Conversely, in

LMICs, the prevalence is slightly higher among younger women but becomes more common among men in older age groups. Although the age-related increase in PAD prevalence is evident in both sexes, the rate of increase is more pronounced in HICs.[2,9] However, epidemiological studies estimating the prevalence of PAD typically use an ABI threshold of <0.9 for diagnosis. In studies that specifically consider symptomatic individuals, the proportion of men is higher than that of women. This discrepancy suggests either a greater disease severity in men or the presence of atypical symptoms in women.[13]

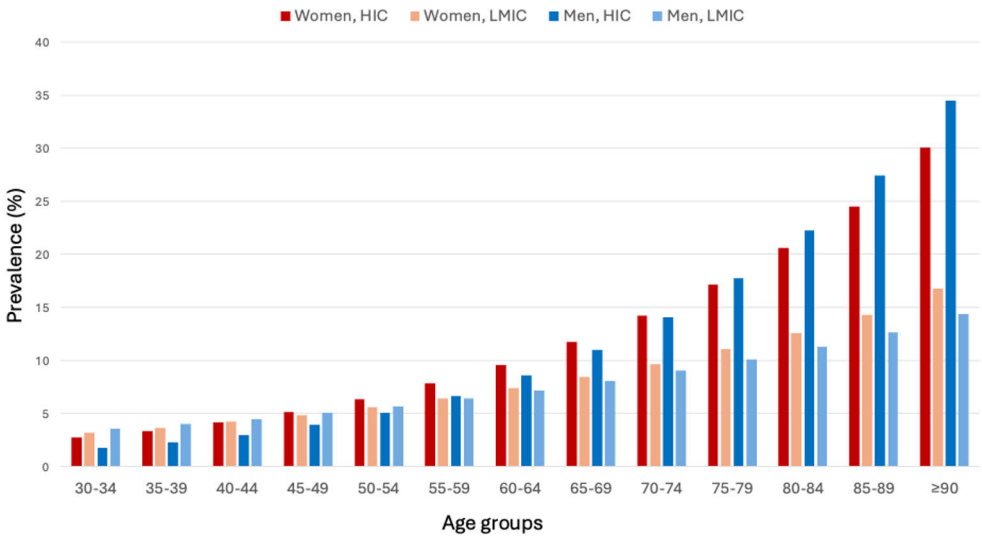


Figure 1. Prevalence of peripheral artery disease in 2015 by age group, sex, and country income level. The data present prevalence percentages for men and women from high-income countries (HICs) and low- and middle-income countries (LMICs), based on a meta-analysis by Song et al. (2019).

It is estimated that up to half of PAD patients are asymptomatic, while only 10–30% exhibit the classical symptoms of intermittent claudication (IC).[14-16] Furthermore, less than 10% of PAD patients represent CLTI.[17,18] Despite the clinical significance of PAD, there is limited data regarding its natural progression. According to meta-analysis, approximately 7 % of patients with asymptomatic PAD develop symptoms over a 7-year period.[19] In a large prospective single-center cohort study involving 1,107 patients without prior revascularizations, the incidence of IC progression to CLTI was observed to be 1.1% over 5 years.[20]

Patients diagnosed with PAD have a markedly reduced life expectancy. Over half of these patients die from CV events, cancer, or diabetes-related complications within 10 years of diagnosis.[21] Asymptomatic and IC patients have a similar risk for CV mortality and morbidity.[22] The prognosis for individuals with CLTI is

particularly poor. These patients are at a markedly elevated risk for fatal or non-fatal CV events, as well as an increased risk of limb loss. Within 1 year of a CLTI diagnosis, approximately 50% of patients survive with both limbs intact, while 20-25% will die and 25% will undergo lower-limb amputation.[23-25] Mortality rates increase to 50% in 5 years.[26] Notably, research has demonstrated that over half of patients undergoing below-knee major amputation for ischemic disease exhibited no symptoms of leg ischemia as recently as 6 months prior.[27] This highlights the unpredictable and often silent progression of PAD in certain patients.

2.1.2 Pathophysiology

The arterial wall consists of three distinct layers: the intima, media, and adventitia. Thickening of the arterial wall leads to a reduction in the lumen diameter, diminishing blood flow and resulting in clinical symptoms. Two distinct pathways of calcification have been identified based on the specific location of calcification within the arterial wall layers. Intimal arterial calcification, commonly referred to as atherosclerosis, has historically been regarded as the most significant form of arterial calcification in PAD. However, in recent years, the role of medial arterial calcification (MAC) in the pathogenesis of PAD has gained increasing attention. Previously regarded as a benign condition with limited clinical significance, MAC is now recognized as a critical contributor to CV pathology, often described as a "silent killer" of the vascular system. Growing interest in MAC and its impact on arterial calcification has led to a deeper understanding of its role in disease progression and CV risk.

2.1.2.1 Atherosclerosis

The pathogenesis of atherosclerosis is a complex, multifaceted process that involves endothelial dysfunction, lipid deposition, inflammatory responses, and the activation of cellular processes, ultimately leading to plaque formation, growth, and instability. Atherosclerotic plaque formation exhibits a tendency to occur in specific regions of the vascular tree, particularly at locations such as bifurcations, branch ostia, and arterial curvatures. These regions are observed to demonstrate increased vulnerability due to the influence of hemodynamic forces, resulting in disturbed flow patterns characterized by low shear stress and oscillatory flow. These conditions contribute to endothelial dysfunction and promote the development of plaque.[28,29]

The process begins with endothelial cell (EC) dysfunction, primarily driven by risk factors that disrupt normal endothelial function, leading to reduced nitric oxide (NO) production.[30] This endothelial dysfunction increases the permeability of the vascular wall, allowing low-density lipoprotein (LDL) particles to infiltrate the

subintimal space. Within the intima, LDL undergoes modification and becomes oxidized, forming oxidized LDL (oxLDL), which has highly atherogenic properties.[31,32] The presence of oxLDL stimulates the upregulation of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), on the surface of EC. These adhesion molecules enable the adherence and subsequent migration of monocytes and T-lymphocytes into the intimal layer, marking a critical step in the early pathogenesis of atherosclerosis.[33]

As monocytes infiltrate the intima, they differentiate into macrophages and begin to engulf oxLDL, eventually transforming into lipid-laden foam cells. The accumulation of foam cells leads to the formation of fatty streaks, which represent the earliest visible lesions of atherosclerosis.[34] Over time, these foam cells undergo apoptosis, releasing their lipid content and further promoting inflammation and necrosis within the plaque. The resultant cellular debris contributes to the formation and expansion of the atherosclerotic plaque, creating an inflammatory microenvironment that perpetuates plaque progression.[35]

The progression of atherosclerosis also involves the migration of vascular smooth muscle cells (VSMCs) from the tunica media into the intimal layer. Once in the intima, VSMCs proliferate and produce extracellular matrix components, contributing to the expansion of the intimal layer and the formation of a fibrous cap over the lipid-rich core of the plaque. This fibrous cap provides a degree of structural integrity to the plaque.[36,37]

The immune response plays a pivotal role in atherogenesis, with macrophages and T-lymphocytes releasing a variety of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These cytokines sustain the inflammatory cycle and recruit additional immune cells to the lesion site, further driving the progression of the plaque.[38] In advanced stages, atherosclerotic plaques consist of a complex composition of smooth muscle cells, inflammatory cells, lipids, connective tissue, and necrotic debris.

The stability of atherosclerotic plaques is a critical factor in the clinical outcomes of atherosclerosis and is influenced by various factors, including the balance between lipid content, necrotic core size, inflammatory processes, and fibrous cap thickness. Plaques characterized by a thin fibrous cap and a large necrotic core are more vulnerable to rupture, which exposes the thrombogenic core material to the bloodstream, leading to platelet activation, thrombosis, and acute clinical events.[39 40]

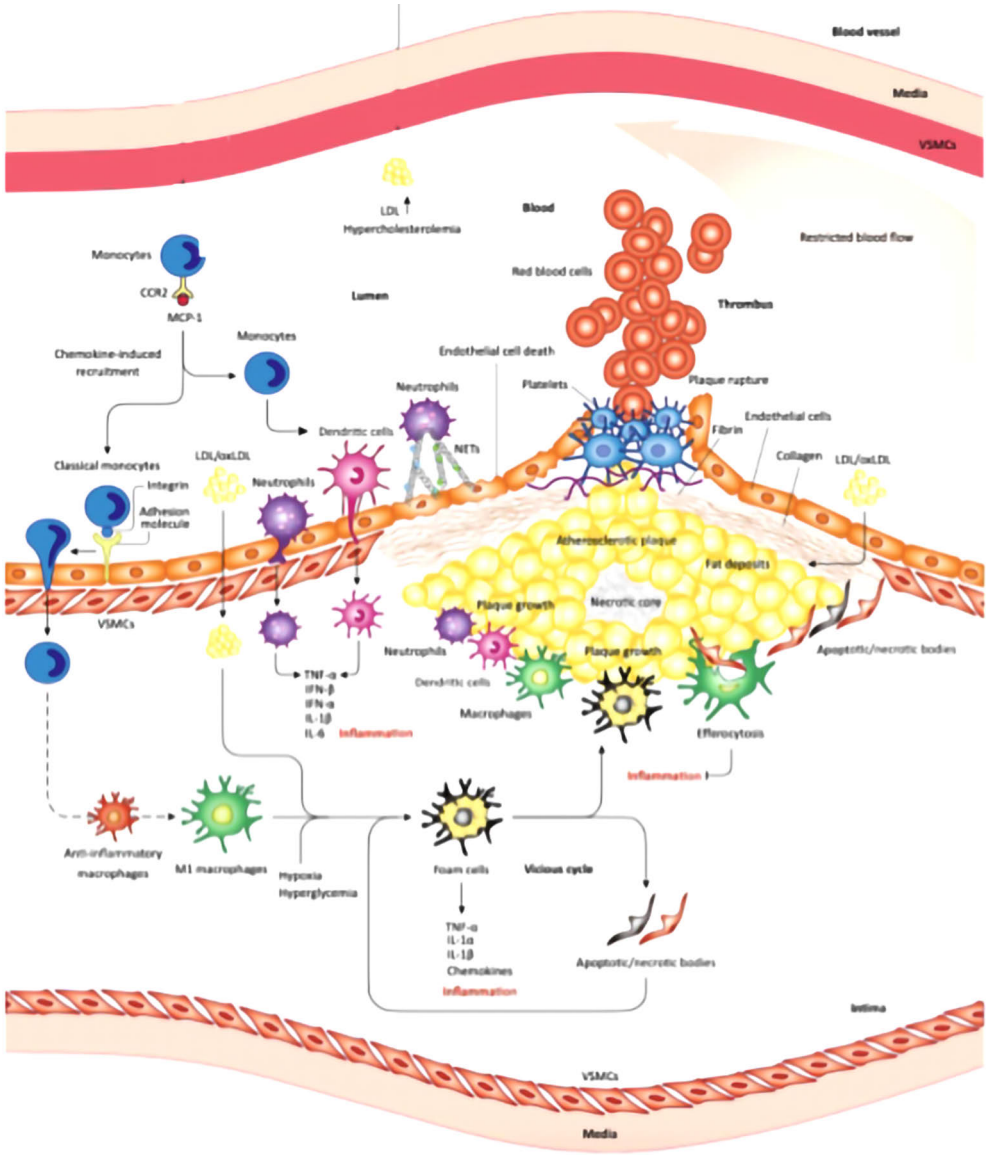


Figure 2. Pathophysiology of atherosclerotic plaque formation into intima. Reproduced with permission from Ajoolabady et al., 2024. ©2024 Springer Nature. Published in Cell Death & Disease.

2.1.2.2 Medial arterial calcification

MAC, also known as Mönckeberg's arteriosclerosis, is associated with age, diabetes, and CKD.[41] These conditions follow different pathways that converge on the same endpoint, MAC, which is characterized by vascular smooth muscle cell osteogenic

transformation, dysregulation of mineral homeostasis, and matrix vesicle (MV) formation leading to calcification of the tunica media.

A key pathological event in MAC is the transformation of VSMCs from their normal contractile phenotype to an osteogenic-like phenotype. While the exact triggers for this transformation are not fully elucidated, several factors have been implicated, including cellular senescence associated with advanced age, hyperphosphatemia in CKD, and accumulation of advanced glycation end products seen in diabetes.[41]

Once VSMCs undergo osteogenic differentiation, mainly driven by runt-related transcription factor 2, they begin to express proteins typically associated with bone formation, such as collagen type I, osteocalcin, and osteopontin. Transformed VSMCs also cause dysregulation of mineral homeostasis, largely due to the loss of calcification inhibitors, such as matrix Gla protein (MGP), inorganic pyrophosphate, fetuin A, and osteoprotegerin. These inhibitors, among multiple others, play protective roles by preventing inappropriate calcification under physiological conditions. Eventually, in MAC, their depletion or functional impairment contributes to unregulated calcium-phosphate accumulation within the medial layer.[42] Warfarin use has been found to accelerate the progression of MAC by inhibiting the activation of MGP.[43]

A hallmark of the calcification process in MAC is the production of mineralization-competent MVs by transformed VSMCs. These MVs serve as critical nucleation sites for the deposition of calcium-phosphate complexes, ultimately leading to the formation of hydroxyapatite, the crystalline structures.[44,45] As MAC advances, calcifications expand and form solid plates that encircle the arterial wall, distorting the structural integrity of the tunica media. This progression is often accompanied by increasing intrusion into the intimal layer and the development of subendothelial hyperplasia.[42] Although it is widely accepted that MAC is primarily confined to the media and not directly linked to luminal stenosis, inward remodeling and thickening of the medial layer may contribute to luminal narrowing.[41,46,47]

Inflammation and increased oxidative stress are believed to play a pivotal role in the progression of MAC, with both CKD and diabetes recognized as chronic inflammatory conditions. Pro-inflammatory cytokines, such as TNF-α, play a central role in the pathophysiology of MAC by accelerating the osteogenic differentiation of VSMCs and degrading the calcification inhibitors. This process is enhanced by oxidative stress, thereby amplifying the cycle of calcification. Additionally, senescent VSMCs are believed to secrete inflammatory cytokines that promote calcification.[48]

MAC is often distributed diffusely throughout the vascular tree, causing indirect, non-occlusive systemic hemodynamic changes. As a result of arterial wall stiffening,

the Windkessel function is impaired, leading to increased pulse pressure, elevated left ventricle afterload, and reduced coronary artery perfusion during diastole.[49,50]

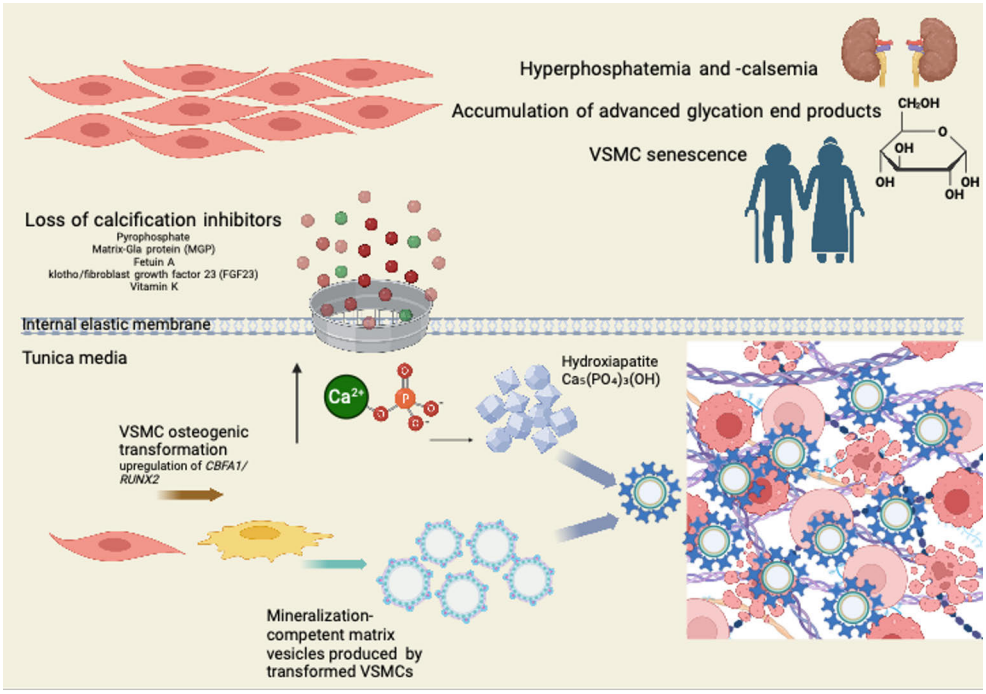


Figure 3. Pathophysiology of MAC. Generated by Biorenter. Kangas 2025

As vessels extend further into peripheral regions and smaller arteries, loss of vessel wall compliance has been linked to blood flow stasis and a reduced autoregulatory response, both of which may contribute to decreased perfusion.[42] At the arteriolar level, stiffening leads to pathological peripheral vasodilation, with peripheral shunting frequently observed. While the exact mechanism behind this shunting remains unclear, a recent study suggests that structural changes in capillaries occur in ischemic extremities, potentially impairing oxygen delivery as a result.[51]

2.1.2.3 Interaction between intimal and medial arterial calcification

Both atherosclerosis and MAC can occur simultaneously in the same arterial segment.[52] The role of MAC in PAD has traditionally been underestimated, as its primary characteristic is not arterial lumen obstruction. However, MAC accelerates the stenotic process associated with atherosclerosis. During the progression of atherosclerosis, the arterial lumen is typically preserved through compensatory

circumferential expansion, known as outward remodeling. However, in the presence of MAC, this compensatory mechanism is disrupted, leading to impaired vascular compliance and promoting inward remodeling. This inward remodeling results in a reduced luminal diameter and increasing vascular resistance, exacerbating ischemic symptoms and contributing to the overall progression of disease. Consequently, the clinical manifestations of PAD are more pronounced and evolve more rapidly when atherosclerosis and MAC are present in the same arterial segment.[47,53]

The presence of MAC below the knee is strongly associated with lower limb amputations[54] and with poorer outcomes in revascularization procedures.[55] O'Neill et al. (2015) investigated the prevalence of MAC among patients with CLTI who had undergone lower limb amputation. They examined the arterial segments from femoral, popliteal, tibial, and dorsalis pedis segments. MAC was present in 72% of the samples, while intimal atheromatous calcification was found in only 23%. Nevertheless, intimal calcification was identified in 68% of samples without lipid accumulation. Direct contact between non-atheromatous intimal calcification and MAC was observed, suggesting that MAC may be a source for this non-atheromatous intimal calcification, with a potential connection along the elastic lamina. Additionally, it was observed that atherosclerotic intimal calcification was not correlated with MAC, in contrast to non-atheromatous intimal calcification.[46] Histopathological studies show that MAC lesions increase in prevalence distally from the proximal popliteal artery, while the presence of intimal atherosclerotic lesions decreases distally.[46,56] Thrombosis leading to luminal occlusion can be induced by both intimal atherosclerotic obstruction and MAC. Narula et al. (2018) investigated histological samples of lower limb arteries from CLTI patients who underwent major amputation. The study revealed that acute or chronic thrombi were present in 72.7% of cases with luminal stenosis exceeding 70%, suggesting that MAC plays a critical role in thrombosis formation, independent of traditional atherosclerotic narrowing.[57]

2.1.3 Risk factors

Atherosclerosis and MAC share common risk factors; however, distinct CV risk factors are associated with each calcification phenotype and the distribution of calcification within the arterial tree.[52,58]

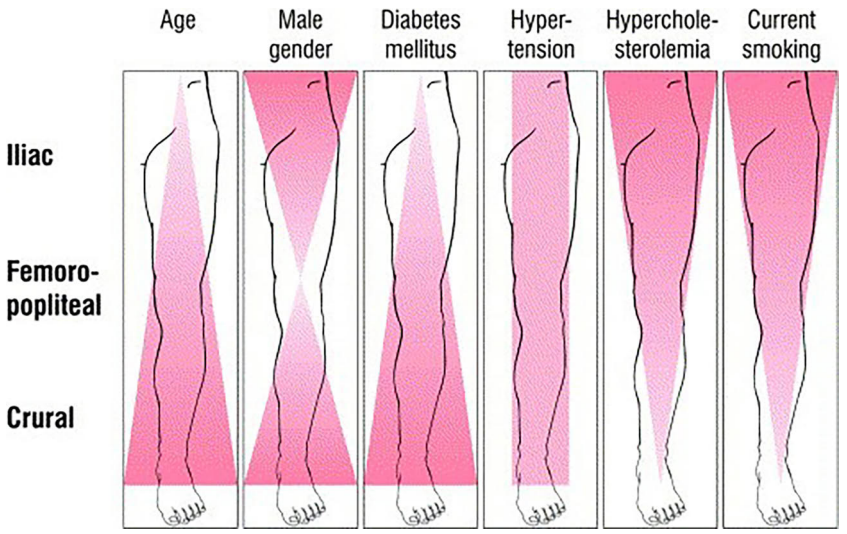


Figure 4. Association of risk factors with the level of PAD. Reproduced with permission from Diehm et al. 2006. ©2006 Elsevier. Published in the European Journal of Vascular and Endovascular Surgery.

2.1.3.1 Smoking

Epidemiological data have consistently shown that smoking is a major risk factor for the development of atherosclerotic disease and is associated with a more proximal form of PAD.[58] Current smoking is associated with a two- to fourfold increased risk of developing PAD compared to nonsmokers. Smoking appears to be particularly associated with the development of PAD compared to other forms of atherosclerotic CV diseases.[59-61] The increase in PAD prevalence is associated with pack-years of smoking, and it appears that the effect of smoking lasts longer for PAD than for other atherosclerotic diseases. The increased risk of PAD after smoking cessation has been shown to persist for up to 30 years, whereas the risk of other atherosclerotic diseases typically returns to the level of never-smokers within 20 years.[60]

2.1.3.2 Diabetes

Diabetes is one of the most important risk factors for PAD, and the presence of diabetes is known not only to increase the incidence of PAD, but also to accelerate the progression of the disease and worsen the severity of the disease and the outcomes of revascularization.[62,63] Among patients with PAD, 20–30% have diabetes.[64] The prevalence of PAD among patients with diabetic foot ulcers is as high as 50%.[65] Consequently, the prevalence of diabetes is particularly high in patients with CLTI, with approximately half of those who undergo revascularization having diabetes.[63] Diabetes is also the strongest risk factor for progression from IC to CLTI.[17] Although

the overall rate of amputations has been declining,[66] the prevalence of amputations among diabetic patients has been increasing.[67] Furthermore, individuals with both PAD and diabetes face a fivefold higher risk of lower extremity amputation compared to non-diabetic PAD patients.[68] There is a linear increase in the risk of PAD with diabetes: every 1% increase in Hemoglobin A1c raises the risk of PAD by 26%.[69] In PAD, arterial changes in diabetic patients are generally more distal than in non-diabetics, with a higher likelihood of tibial arterial involvement.[68] Diabetes is recognized as a common risk factor for both atherosclerotic lesions and MAC.[62,70] Notably, the incidence of MAC in the lower extremities among individuals with diabetes is approximately four times higher than in healthy subjects.[71]

2.1.3.3 Hypertension

Hypertension is an independent risk factor for PAD,[9] although its impact on PAD is less pronounced compared to its role in other CV diseases. Nevertheless, it significantly influences the prognosis of individuals with PAD by increasing the risk of CV events.[72] While the association between hypertension and PAD is weaker compared to smoking and diabetes,[61,73] elevated systolic blood pressure is particularly linked to a higher risk of PAD.[74,75] The pathophysiological connection between hypertension and PAD is primarily driven by increased mechanical stress on the vascular endothelium due to elevated blood pressure, which induces endothelial dysfunction—a key precursor to atherosclerosis.[76]

2.1.3.4 Dyslipidemia

A standard lipid panel includes total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and the LDL-HDL ratio. Dyslipidemia, characterized by elevated levels of LDL and low levels of HDL, is strongly associated with the progression of atherosclerosis. Compared to coronary artery disease (CAD), the lipid profiles associated with PAD are less extensively studied. However, dyslipidemia seems to be a weaker risk factor for PAD than for CAD or cerebrovascular disease (CeVD), and differences between the lipid profiles associated with PAD and CAD have also emerged.[77]

HDL levels are inversely associated with PAD prevalence,[77-79] and high HDL levels have been shown to offer protection against PAD.[74] However, the total cholesterol/HDL ratio appears to be the strongest predictor of PAD.[78,79]

The existing literature does not provide a substantial body of evidence that LDL is associated with PAD. While some epidemiological studies have reported an association between LDL and PAD,[78,80] other studies have produced conflicting results.[77,79] However, lipid-lowering therapies and reduction in LDL levels appear

effective in decreasing the risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE) in PAD patients.[78,81,82] Additionally, there is no clear consensus on the relationship between triglyceride levels and PAD. However, a recent meta-analysis suggested that elevated triglyceride concentrations may be associated with both the prevalence and severity of PAD.[83]

2.1.3.5 Chronic kidney disease

Matsushi et al. (2017) conducted a meta-analysis to assess the risk of PAD in patients with CKD. After adjusting for traditional CV risk factors, the hazard ratio (HR) for PAD ranged from 1.22 to 2.06, depending on the estimated glomerular filtration rate (eGFR). The analysis demonstrated a gradual increase in PAD risk with declining eGFR values below 60 mL/min, whereas the risk remained stable in individuals with eGFR values at or above this threshold.[84] Similar results have been observed by Wattanakit et. al (2007). They found that in a multivariable model including classical atherosclerotic risk factors, CKD was significantly associated with PAD, with a HR of 1.56.[85] The prevalence of PAD increases gradually with the severity of CKD.[84,86,87] CKD leads to impaired calcium-phosphate metabolism[88] and is associated with accelerated calcification in both the intimal[89] and medial[90] layers. In patients with CKD, intimal atherosclerotic plaques are heavily calcified, whereas in the absence of CKD, plaques are more often fibroatheromatous. MAC is considered to be the predominant form of arterial calcification in CKD.[91]

2.1.3.6 Age

Many risk factors for PAD, such as hypertension, diabetes, high cholesterol, and smoking, tend to accumulate over time. As people age, they are more likely to have had prolonged exposure to these risk factors, increasing their likelihood of developing PAD. According to data from the National Health and Nutrition Examination Survey (NHANES), the prevalence of PAD rises dramatically with the accumulation of risk factors; individuals with three or more risk factors have a tenfold increase in the odds ratio (OR) for PAD.[92] A similar cumulative effect of risk factors was reported in a meta-analysis by Joosten et al. (2012).[93] Aging itself is also an independent risk factor for PAD. With age, cellular function slows and declines, cell proliferation decreases, apoptosis accelerates, DNA repair weakens, and both epigenetic changes and telomere dysfunction contribute to the development of atherosclerosis.[94] Similarly, cellular senescence promotes changes associated with MAC.[41]

2.1.3.7 Metabolic syndrome

Metabolic syndrome (MetS) is defined by the presence of abdominal obesity, plasma fasting glucose, hypertriglyceridemia, reduced HDL cholesterol, and hypertension. It is considered a prothrombotic and pro-inflammatory condition.[95] Excluding obesity, each individual component of MetS is an established independent risk factor for PAD. Multiple studies have demonstrated a correlation between MetS and an increased risk of CAD, ischemic stroke, and CV mortality.[96-98] Consequently, it is not surprising that MetS has been found to be positively associated with a heightened risk of developing PAD, with the likelihood rising in proportion to the number of MetS components present.[99,100] Over the past few decades, obesity has become a global pandemic, with most deaths related to high body mass index (BMI) being attributed to CV disease.[101] Nevertheless, elevated BMI does not independently appear to significantly increase the risk of CV disease. It is therefore likely that the metabolic disorders associated with MetS and high BMI are the primary contributors to the increased risk of CV disease.[102]

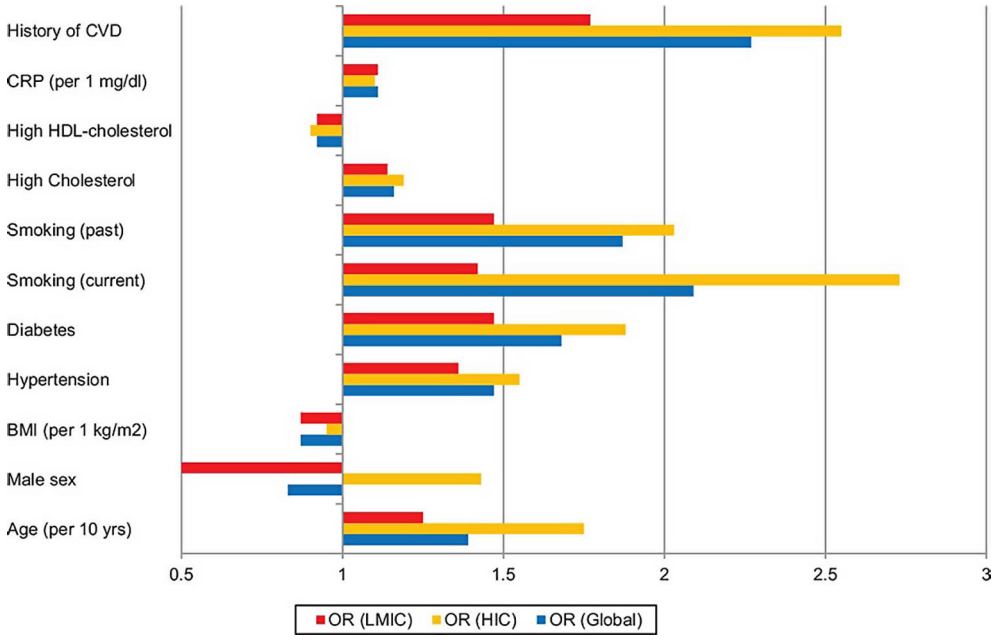


Figure 5. Odds ratios of risk factors for PAD. Adapted from: Criqui et al., 2015. Reproduced with permission from Criqui and Aboyans, 2015. ©2015 American Heart Association. Published in Circulation Research.

2.1.4 Polyvascular disease

The presence of PAD not only signifies localized atherosclerosis within the peripheral vasculature but also serves as a marker of systemic atherosclerosis, indicating a broader CVD burden. Individuals with PAD face a substantially elevated risk of CV morbidity and mortality, and studies have consistently demonstrated that patients with PAD have a two- to threefold increased risk of myocardial infarction, stroke, and CV-related mortality compared to those without the disease.[103] Despite a significant decline in CV mortality over recent decades, this trend has not been uniform among PAD patients, as they continue to experience disproportionately high rates of MACE.[21,104,105] Secondary prevention strategies, which are well-established for CAD, remain underutilized in PAD patients, despite clinical guidelines recommending aggressive risk factor management.[106] Among individuals with PAD, CV death accounts for 60% of total mortality, highlighting the systemic nature of atherosclerosis.[107]

Patients with PAD often have coexisting CAD and/or CeVD, with approximately half affected by one or both conditions.[108] The term polyvascular disease describes the presence of CV disease involvement in two or more vascular territories, signifying a more extensive disease phenotype.[109] A landmark study from the Reduction of Atherothrombosis for Continued Health (REACH) registry provided pivotal insights into the prognostic significance of polyvascular disease. It demonstrated that patients with CV disease affecting multiple vascular beds have the highest risk of MACE.[110] Subsequent studies have reinforced this finding, consistently showing that the risk of MACE escalates with the number of affected vascular territories.[111-115] Among polyvascular disease subtypes, patients with concurrent PAD and CAD face a higher risk of MACE compared to those with CAD and CeVD. Additionally, when comparing these vascular diseases in isolation, patients with PAD exhibit the highest all-cause mortality rates. This observation suggests that PAD may be a marker of a more extensive CV disease burden.[116,117]

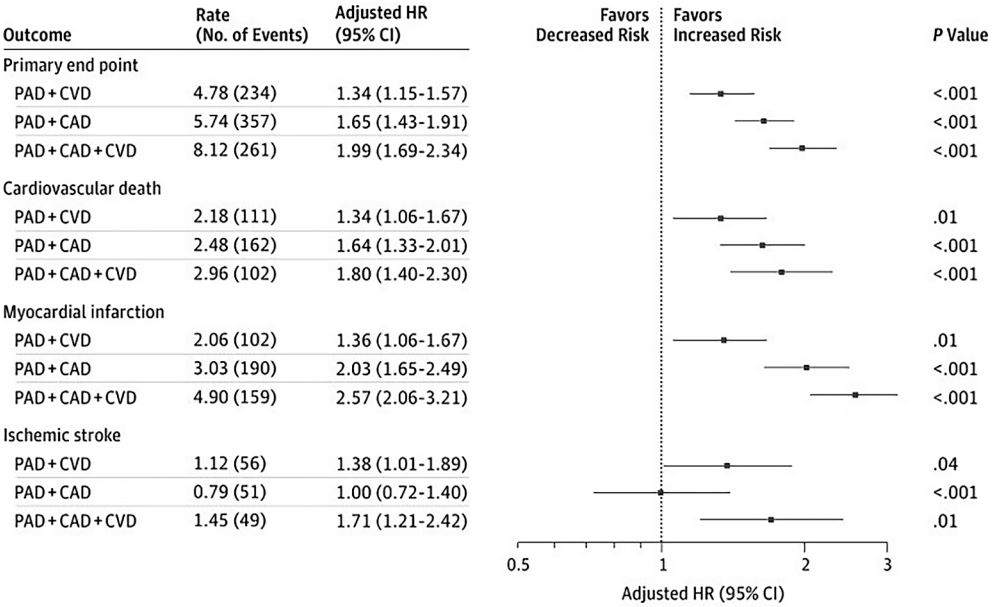


Figure 6. Cardiovascular events according to polyvascular disease. Reproduced with permission from Gutierrez and Mulder, 2018. ©2018 American Medical Association. Published in JAMA Network Open.

2.1.5 Pharmacological treatment of PAD

The cornerstone of pharmacological management in PAD includes lipid-lowering and antithrombotic therapies. Despite the well-documented benefits of pharmacological treatment, its implementation remains suboptimal among PAD patients.[14] Due to the polyvascular nature of PAD, pharmacological treatment primarily aims to prevent CV events, with a secondary focus on improving limb prognosis.

2.1.5.1 Cardiovascular risk factors

The role of lipid-lowering therapy in CV prevention, including PAD, is well established. Although most research has focused on CAD, statins have become integral to PAD management as well. The Heart Protection Study demonstrated that statins reduced coronary events by 21%, coronary revascularization procedures by 30%, and ischemic stroke by 26% among PAD patients.[81] Additionally, a systematic review and meta-analysis by Kokkinidis et al. (2020) demonstrated that statin therapy significantly reduced the risk of major amputation in patients with CLTI. Furthermore, a subgroup analysis of PAD patients from the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With

Elevated Risk) trial confirmed that PCSK9 inhibitor therapy along with statins not only reduced MACE but also significantly decreased limb-related events.[118]

Unlike coronary plaques, which are rich in lipid cores, PAD plaques often exhibit extensive fibrosis and calcification, making LDL lowering potentially less influential on plaque progression.[119] Statins reduce LDL deposition in the subintimal space, decreasing inflammation and slowing plaque progression. They also exert pleiotropic effects, including plaque stabilization, systemic anti-inflammatory action, improved vascular tone, and reduced platelet aggregation. Additionally, statins reinforce the fibrous cap of atherosclerotic plaques, lowering rupture risk, and inhibit the migration and proliferation of VSMCs.[120]

Diabetes accelerates atherosclerosis and increases the risk of PAD, and glycemic control is crucial for reducing macrovascular complications. The risk of PAD increases progressively with diabetes: for each 1% rise in Hemoglobin A1c, the likelihood of developing PAD increases by 26%.[69] The target blood pressure for these individuals is a systolic pressure below 130 mm Hg and a diastolic pressure under 80 mm Hg. Antihypertensive therapy should be administered to achieve these goals and diminish the risk of MACE. Selective use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is recommended, given their efficacy in reducing CV events in this cohort.[5]

2.1.5.2 Antithrombotic therapy

Antiplatelet agents improve prognosis in PAD by reducing thrombotic risk, inflammation, and endothelial dysfunction. They inhibit platelet aggregation in irregular arterial walls, where blood flow is reduced, and luminal narrowing creates an environment conducive to thrombus formation.[121] In addition to their antithrombotic effects, antiplatelets also modulate vascular inflammation and endothelial function. For example, acetylsalicylic acid (ASA) inhibits prostaglandin synthesis by blocking COX-1, while P2Y12 inhibitors, most notably clopidogrel in vascular surgical practice, can reduce leukocyte recruitment and improve endothelial NO bioavailability, collectively leading to improved vasodilation and microvascular perfusion.[122,123]

The role of antiplatelet therapy (mostly ASA) in reducing vascular events in patients was first highlighted in the Antiplatelet Trialists' Collaboration meta-analysis, which demonstrated a 23% reduction in non-fatal strokes, myocardial infarctions, and vascular deaths among patients with PAD.[124] The CAPRIE trial, which compared single antiplatelet therapies (clopidogrel vs. ASA) in PAD patients, showed a 23.8% relative risk reduction in MACE in favor of clopidogrel, with similar bleeding profiles.[125] Additionally, a meta-analysis found no benefit of the P2Y12 inhibitor ticagrelor over clopidogrel in reducing CV events among PAD

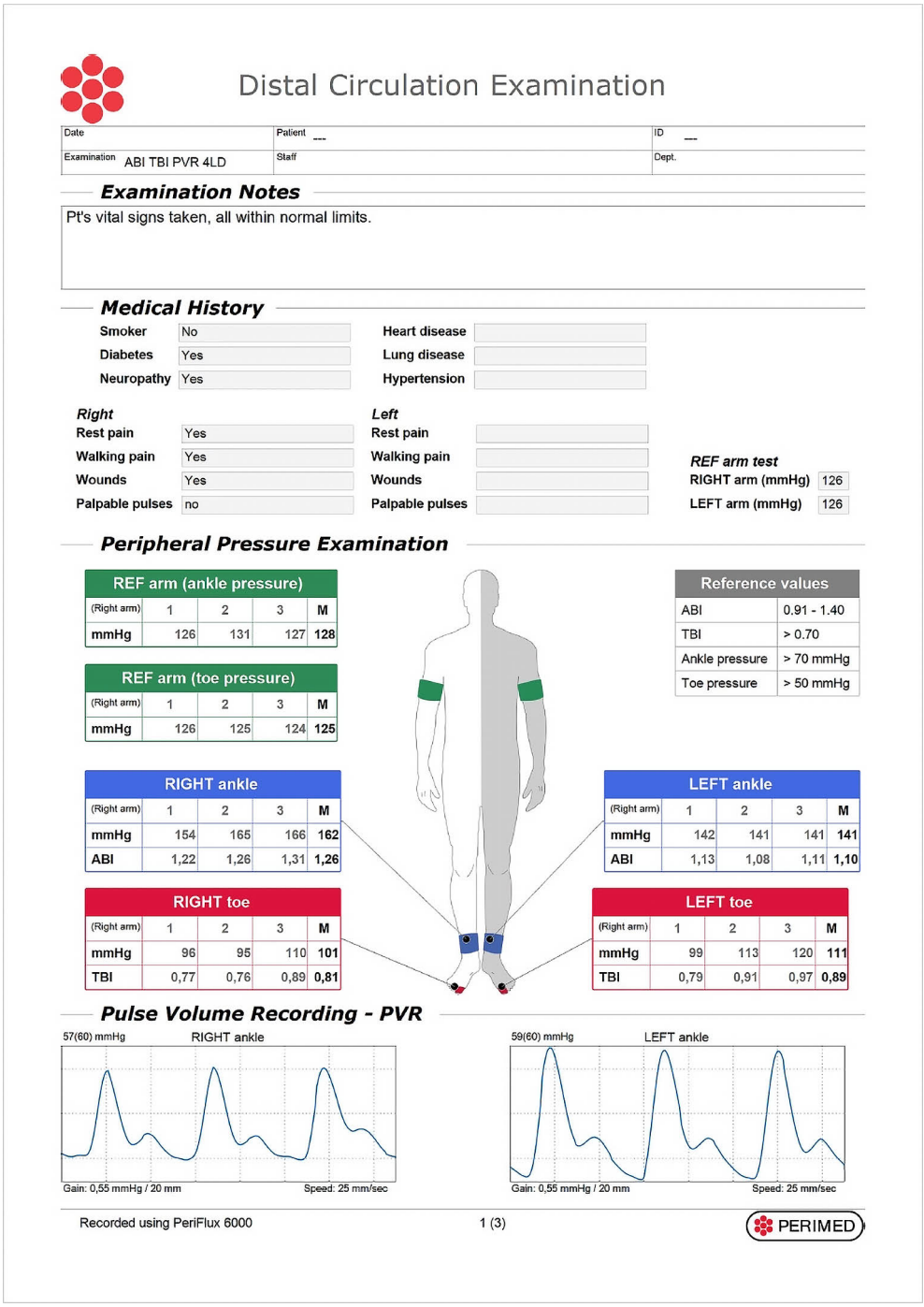
patients.[126] Recent trials have further investigated the potential benefits of rivaroxaban in high-risk PAD patients. The COMPASS trial demonstrated that the combination of low-dose rivaroxaban and aspirin resulted in a 31% reduction in MACE and MALE compared to aspirin alone in PAD patients.[127] Similarly, the VOYAGER PAD trial, which focused on patients undergoing lower extremity revascularization, found that the addition of low-dose rivaroxaban to aspirin led to a 15% reduction in MACE and MALE relative to aspirin monotherapy. Despite these benefits in CV and limb-related outcomes, neither trial observed a significant reduction in all-cause mortality. Although both trials reported an increased incidence of major bleeding in the rivaroxaban arms according to the International Society on Thrombolysis and Haemostasis (ISTH) classification, neither study observed a significant increase in fatal bleeding or intracranial hemorrhage.[127,128]

ASA or clopidogrel are the first-line treatments for the secondary prevention of thrombotic events in patients with symptomatic PAD and should be administered unless contraindicated. Current evidence supports their use in reducing CV morbidity and mortality in this population. However, there is no high-quality evidence to support the routine use of antiplatelet therapy for primary prevention in asymptomatic individuals with PAD.[125,129]

2.2 Non-invasive pressure measurements

TBI and ABI measurements are essential and widely utilized methods for the non-invasive assessment of PAD. The ABI is determined by measuring systolic blood pressure (SBP) at the brachial artery in the upper arm and at the dorsalis pedis or posterior tibial arteries in the ankles. The ankle SBP is then divided by the brachial SBP to calculate the ABI ratio. Similarly, the TBI is obtained by measuring SBP at the toes and comparing it to the brachial SBP to derive the ratio. At the same time, absolute ankle and TP values are recorded. These measurements can be performed manually or using advanced techniques, such as photoplethysmography and laser Doppler methods, which enhance accuracy. Both photoplethysmography and laser Doppler are applied in the assessment of both ankle and TP, ensuring precise evaluation, particularly in patients with vascular calcifications or compromised peripheral circulation.

A normal ABI value is typically greater than 1, indicating that the SBP is higher at the ankle than at the arm. As the blood pressure waveform moves further from the heart, there is an amplification effect, with SBP rising and diastolic pressure dropping. This amplification is largely attributed to retrograde wave reflection from the resistance of distal arterioles, which adds to the forward-moving wave.[130] Indeed, taller individuals have been observed to have higher ABIs, reflecting a more pronounced amplification effect.[131] Under normal circumstances, the absolute systolic TP is about 20–40 mmHg lower than the corresponding ankle pressure.[132]



Distal Circulation Examination

Date	Patient ---	ID ---
Examination ABI TBI PVR 4LD	Staff	Dept.

Examination Notes

Pt's vital signs taken, all within normal limits.

Medical History

Smoker	No	Heart disease	
Diabetes	Yes	Lung disease	
Neuropathy	Yes	Hypertension	

Right		*Left*	
Rest pain	Yes	Rest pain	
Walking pain	Yes	Walking pain	
Wounds	Yes	Wounds	
Palpable pulses	no	Palpable pulses	

REF arm test

RIGHT arm (mmHg)	126
LEFT arm (mmHg)	126

Peripheral Pressure Examination

REF arm (ankle pressure)				
(Right arm)	1	2	3	M
mmHg	126	131	127	**128**

REF arm (toe pressure)				
(Right arm)	1	2	3	M
mmHg	126	125	124	**125**

Reference values	
ABI	0.91 - 1.40
TBI	> 0.70
Ankle pressure	> 70 mmHg
Toe pressure	> 50 mmHg

RIGHT ankle				
(Right arm)	1	2	3	M
mmHg	154	165	166	**162**
ABI	1,22	1,26	1,31	**1,26**

LEFT ankle				
(Right arm)	1	2	3	M
mmHg	142	141	141	**141**
ABI	1,13	1,08	1,11	**1,10**

RIGHT toe				
(Right arm)	1	2	3	M
mmHg	96	95	110	**101**
TBI	0,77	0,76	0,89	**0,81**

LEFT toe				
(Right arm)	1	2	3	M
mmHg	99	113	120	**111**
TBI	0,79	0,91	0,97	**0,89**

Pulse Volume Recording - PVR

Recorded using PeriFlux 6000 1 (3) PERIMED

Figure 7. Report of pressure measurements with PeriFlux 6000. Source: Perimed, www.perimed-instruments.com

2.2.1 Ankle-brachial index

Over the years, the ABI has been recognized not only as a key diagnostic parameter for PAD but also as an independent prognostic marker of overall CV status and disease burden. A low, borderline or abnormally high ABI is associated with an increased risk of CV events. Hence, the ABI measurement is invaluable for identifying individuals at higher risk of CV morbidity and mortality. Furthermore, the ABI is often combined with other risk assessment, such as the Framingham Risk Score, to provide a more comprehensive picture of a patient's CV burden.[6]

2.2.1.1 Low ABI

An ABI value ≤0.90 is a commonly employed diagnostic criterion in both clinical and epidemiological settings, used to diagnose both symptomatic and asymptomatic PAD. According to review articles by Dachun et al. (2010) and Herraiz-Adillo (2020), the specificity of ABI≤0.90 for detecting arterial stenosis of at least 50% was 83.3–99.0% and 92%, respectively. Nevertheless, the same studies reported that the specificity of the ABI remained relatively low, at 15–79% and 61%, respectively.[133,134] The sensitivity was particularly low in elderly individuals and patients with diabetes.[133,135]

The literature provides strong evidence that a low ABI is associated with adverse outcomes, both in the general population and among high-risk CV groups. Several meta-analyses have consistently shown associations between low ABI and increased CV morbidity, mortality, and total mortality. A meta-analysis consisting of 43 observational cohort studies involving 94,254 participants reported that a low ABI (<0.9) was associated with significant risk increases: RR 2.52 for all-cause mortality, 2.94 for CV mortality, 2.17 for cerebrovascular events, 2.28 for myocardial infarction, 2.81 for fatal myocardial infarction, and 2.28 for fatal stroke (all P<0.00001).[103] Another meta-analysis of 11 longitudinal studies of general populations, encompassing 44,590 participants, provided pooled age, sex, CV risk factors and prevalent CV disease adjusted estimates, showing that ABI<0.9 was associated with an RR of 1.60 (95% Confidence Interval (CI) 1.32–1.95) for all-cause mortality, 1.96 (95% CI 1.46–2.64) for CV mortality, 1.45 (95% CI 1.08–1.93) for CAD, and 1.96 (95% CI 1.10–1.65) for stroke.[136] A meta-analysis of 19 pooled studies examined mortality among patients diagnosed with PAD through ABI screening, using a threshold of ABI<0.9 in most studies. The analysis reported an HR of 2.99 (95% CI, 2.16–4.12) for all-cause mortality and 2.35 (95% CI, 1.91–2.89) for CV mortality.[137] Similarly, another meta-analysis of 16 epidemiological studies, involving 48,294 adults from the general population, found that ABI<0.90 was associated with a 10-year CV mortality rate of 18.7% in men and 12.6% in women. In contrast, individuals with ABIs between 1.10 and 1.40 had significantly lower 10-year CV mortality rates, at

4.4% for men and 4.1% for women. This increased risk remained substantial even after adjusting for traditional CV risk factors based on the Framingham Risk Score, with an HR of 4.2 for men and 3.5 for women.[6]

The risk for CV and all-cause mortality rises as ABI values decrease, with a progressive decline in ABI over time further elevating this risk. In a follow-up study, an ABI reduction of more than 0.15 over a 3-year period was associated with a risk ratio (RR) of 2.4 (95% CI 1.2–4.8) for all-cause mortality and 2.8 (95% CI 1.3–6.0) for CV mortality.[138] Additionally, the degree of ABI reduction correlated with a heightened risk of CV events and all-cause mortality.[139] Another follow-up study, using a Cox regression model adjusted for risk factors, showed a linear increase in mortality risk across lower ABI categories: for ABI 0.7–0.89, the HR was 1.7 (95% CI 1.2–2.4), and for ABI<0.5, the HR was 3.6 (95% CI 2.4–5.4).[140]

2.2.1.2 Borderline ABI

An ABI value <0.9 is widely recognized as a diagnostic criterion for PAD; however, its effectiveness in risk stratification for mortality and CV events remains suboptimal. As a result, an ABI range of 0.9–1.0 is often classified as "borderline ABI". Growing evidence suggests that borderline ABI is a clinically relevant marker for predicting adverse CV outcomes, underscoring its importance in comprehensive CV risk assessment.

One of the most critical observations in the Cardiovascular Health Study (2006) was that individuals with a low normal ABI (0.9–1.0) had significantly increased CV and all-cause mortality compared to those with an ABI between 1.1 and 1.2.[141] Supporting this, a meta-analysis of 16 studies confirmed that an ABI of 0.9–1.0 is associated with an increased risk of CV and all-cause mortality.[6] In light of these findings, the American Heart Association revised the classification of normal ABI values and introduced the category of borderline ABI.[142] More recently, Tanaka et al. (2016) showed in a cohort study (N=19,994) that patients with borderline ABI values (0.91–1.00) had increased CV and all-cause mortality compared to those with a normal ABI (1.01–1.39). The HR for all-cause mortality was 2.27 (p=0.005) and for CV mortality it was even higher at 3.47 (p=0.003). Patients with a borderline ABI also had a greater burden of comorbidities.[143] Conversely, a follow-up study published in 2019, with a mean duration of 8.7 years and including 3,786 individuals, revealed no statistically significant differences in MACE, CV mortality, or all-cause mortality between individuals with a borderline ABI (0.9–0.99) and those with a normal ABI (1.0–1.39).[144] The absence of an association between borderline ABI and MACE, as well as CV events, can be attributed to the fact that the study was conducted within a Mediterranean population, with patients who had previously experienced CV events being excluded from the study.

A follow-up study of a general population cohort without a prior PAD diagnosis revealed that individuals with a borderline ABI had a twofold risk of undergoing ischemic leg amputation compared to those with an ABI of 1.1–1.2.[145] In a 5-year follow-up study, patients with a borderline ABI demonstrated a significantly greater risk of functional decline compared to those with a normal ABI (1.1–1.3), and their rate of decline was comparable to individuals with an ABI between 0.7 and 0.89.[146] Additionally, individuals with a borderline ABI have a significantly higher risk of developing PAD in the future compared to those with a normal ABI.[144]

2.2.1.3 Abnormally high ABI

An ABI greater than 1.3 or 1.4 is regarded as abnormally high, and recent guidelines have recommended adjusting the cut-off to 1.4. It is thought that MAC has a substantial impact on tibial artery compressibility, requiring increased pressure to achieve arterial occlusion and leading to falsely elevated ABI results. In some cases, the tibial arteries are non-compressible, making it impossible to determine the ABI. The prevalence of PAD among patients with an abnormally high ABI is remarkable, over half of these individuals having PAD.[147] Patients with an abnormally high ABI are at increased risk for foot ulcers, lower-limb amputations, and a reduced quality of life.[148,149]

Mortality rates follow a U-shaped distribution across the ABI spectrum, as noted in multiple studies.[6,141,150] CV and all-cause mortality among individuals with an abnormally high ABI have been reported to be comparable to those with ABI<0.9. However, findings regarding the association between high ABI values and elevated CV mortality risk have been inconsistent, and some studies have found no significant association. It is hypothesized that arterial stiffness resulting from MAC, which contributes to elevated ABI values, may play a role in increasing the risk of adverse CV outcomes.

A meta-analysis of 18 longitudinal studies, encompassing 60,467 individuals, found a heightened pooled RR of 1.84 (95% CI 1.54–2.20) for CV and 1.45 (95% CI 1.16–1.82) for all-cause mortality, with abnormally high ABI values (>1.3 or >1.4) in the general population compared to normal ABI. In the same study, the RR among CKD patients with abnormally high ABI values was 4.28 (95% CI 2.18–8.40) for CV mortality and 1.67 (95% CI 1.03–2.71) for all-cause mortality.[151] In another meta-analysis focusing on CKD patients, including six studies with 5,820 patients, the pooled HRs were 4.04 (95% CI 1.82–8.95) for CV mortality and 1.94 (95% CI 1.02–3.68) for all-cause mortality among patients with ABI>1.3 compared to normal ABI. The corresponding HRs for patients with a low ABI (<0.9) were 5.18 (95% CI 2.97–9.04) for CV mortality and 2.45 (95% CI 1.27–4.73) for all-cause mortality.[152]

In the Strong Heart Study, which included an 8-year follow-up, individuals with a high ABI (>1.4) had an adjusted RR of 1.77 (95% CI 1.48–2.13) for all-cause

mortality compared to those with a normal ABI. For individuals with a low ABI (<0.9), the adjusted RR for all-cause mortality was 1.69 (95% CI 1.34–2.14). Regarding CV mortality, the adjusted RRs were 2.09 (95% CI 1.49–2.94) for high and 2.52 (95% CI 1.74–3.64) for low ABI values.[150] Similarly, Laivuori et al. (2021) observed reduced survival rates in an age- and sex-adjusted model among patients with a high ABI (>1.3), reporting an HR of 2.2 (95% CI 1.9–2.6). In comparison, the HR was 1.5 (95% CI 1.4–1.7) for patients with ABI<0.5 and 1.1 (95% CI: 1.0–1.2) for those with an ABI of 0.5–0.89.[153] A recent study using data from the NHANES cohort reported that, over a 15-year follow-up period, individuals with a high ABI (>1.4) had mortality rates comparable to those with ABI<0.9 in multivariable analysis. The HR for CV mortality associated with a high ABI was 2.58 (95% CI 2.11–3.14), while the HR for all-cause mortality was 2.49 (95% CI 2.22–2.79). For comparison, in the same study, for individuals with a low ABI (<0.9), the corresponding HRs were 2.91 (95% CI 2.17–3.89) for CV mortality and 2.60 (95% CI 2.18–3.09) for all-cause mortality.[154]

However, several studies have indicated that the association between high ABI and CV mortality becomes non-significant after adjusting for CV risk factors. For example, in a Cardiovascular Health Study, a 10-year follow-up showed that ABI>1.4 was associated with an increased risk for all-cause mortality (HR 1.57, 95% CI 1.07–2.31) in an adjusted model but was not significantly associated with CV mortality. Suominen et al. (2010) reported comparable ORs for high (≥1.3) and low ABI (<0.5) in relation to all-cause mortality: 2.34 (95% CI 1.31–4.19) for high ABI and 2.38 (95% CI 1.75–3.23) for low ABI. For patients with ABI≤0.9, the OR was 1.75 (95% CI 1.34–2.28). All values were adjusted for PAD risk factors and compared to the reference group with a normal ABI (>0.9 to <1.3). However, for high ABI the CV mortality was no longer significant after multivariable adjustments.[155] In the population-based Multi-Ethnic Study of Atherosclerosis, Criqui et al. (2011) demonstrated a similarly increased risk for incident CAD, stroke or CV mortality in individuals with ABI≥1.40 or <1.00. However, in the adjusted model, the association was no longer significant for the ABI≥1.40 group.[156]

2.2.2 Toe brachial index and toe pressure

In recent years, the diagnostic importance of TBI and TP for PAD has increased, particularly in specific patient groups such as those with MAC resulting from diabetes and CKD.[4] Approximately one-fifth of PAD patients have a normal ABI but a low TBI,[157] and up to 29% of CLTI patients have a normal ABI but a low TP <30 mmHg.[158] In such patients, the sensitivity of ABI is reduced due to MAC, which causes falsely elevated readings because of incompressible arteries. Recently published guidelines for the management of PAD emphasize the importance of TBI

as a first-line diagnostic tool alongside ABI in patients with a normal or abnormally high ABI but a clinical suspicion of PAD.[5,159]

2.2.2.1 Low toe brachial index and toe pressure

According to guidelines, TBI≤0.70 is considered abnormal, whereas TBI>0.7 is considered normal.[5,23,132,159] The sensitivity of TBI in detecting arterial stenosis of 50% or greater is significantly superior to that of ABI, with a sensitivity of 81%, although its specificity is slightly lower at 77%.[134] This aligns with findings showing that among patients with a clinical suspicion or confirmed diagnosis of PAD, 20.5% had a low TBI (<0.70) despite a normal ABI (>0.90).[157] Furthermore, in accordance with the Wound, Ischemia, and Foot Infection (WIfI) classification, TP<60 mmHg is considered indicative of diminished perfusion. TP≤30 mmHg, in conjunction with clinical manifestations, is regarded as diagnostic of CLTI.[132,160]

In contrast to ABI, the diagnostic thresholds for TBI and TP in predicting CV morbidity, mortality, and overall mortality have yet to be fully validated in large-scale screening trials. However, several studies report that low TBI and TP are associated with increased mortality. Hyun et al. (2014) reported an increased risk for CV mortality among patients with a TBI (<0.62) compared to those with a normal TBI (0.62–1.08), with HRs of 1.62–2.65 depending on the TBI group.[161] Wickström et al. (2017) found even worse estimates for CV mortality in both low TBI and TP groups: the HR was 3.68 (95% CI 1.48–9.19) in the TBI<0.25 group compared to TBI≥0.5, and 2.84 (95% CI 1.75–4.61) in the TP<30 mmHg group compared to TP≥50 mmHg.[162] Another study by Wickström et al. (2019) demonstrated that patients with bilaterally decreased TP (<30 mmHg) and TBI (TBI<0.3) had particularly poor survival outcomes.[7]

In a study by Laivuori et al. (2021), among patients with a normal ABI (0.9–1.3), low TP (<50 mmHg) was associated with a significantly increased 10-year all-cause mortality rate of 80.4%, compared to 51.6% in patients with normal TP levels (≥80 mmHg).[153] In a similar setting, Hishida et al. (2020) examined all-cause mortality estimates for patients with a normal or high ABI (>0.9) but low TBI. Mortality was significantly higher in the population with TBI≤0.6 compared to those with TBI>0.6, and the results remained similar with a higher TBI cut-off (TBI≤0.7 vs. TBI>0.7).[163]

Patients with low TBI and TP have also been observed to experience worse limb outcomes compared to those with a normal TBI. In a cohort study of 261 patients, Sonter et al. (2015) examined foot complications and found that patients with a low TBI (<0.7) were 19 times more likely to have a history of foot complications compared to those with a normal TBI (≥0.7).[164] TP<30 mmHg is predictive of a high probability of major amputation and is an adverse prognostic indicator for optimal wound healing.[160,165]

2.3 Intracranial aneurysms

Intracranial aneurysm (IA) is defined as a pathological dilatation of the cerebral arteries, with variations in size, configuration, and location. IAs often occur at arterial bifurcations where the vessel wall is structurally predisposed to weakness and are typically found within the circle of Willis, a key vascular structure at the base of the brain. The most common form of IA is a saccular aneurysm, also known as a berry aneurysm, which is characterized by a sac-like outpouching arising from a focal area of the vessel wall. The underlying pathophysiological mechanisms of aneurysm formation and rupture are complex and involve a combination of genetic, hemodynamic, and environmental factors.

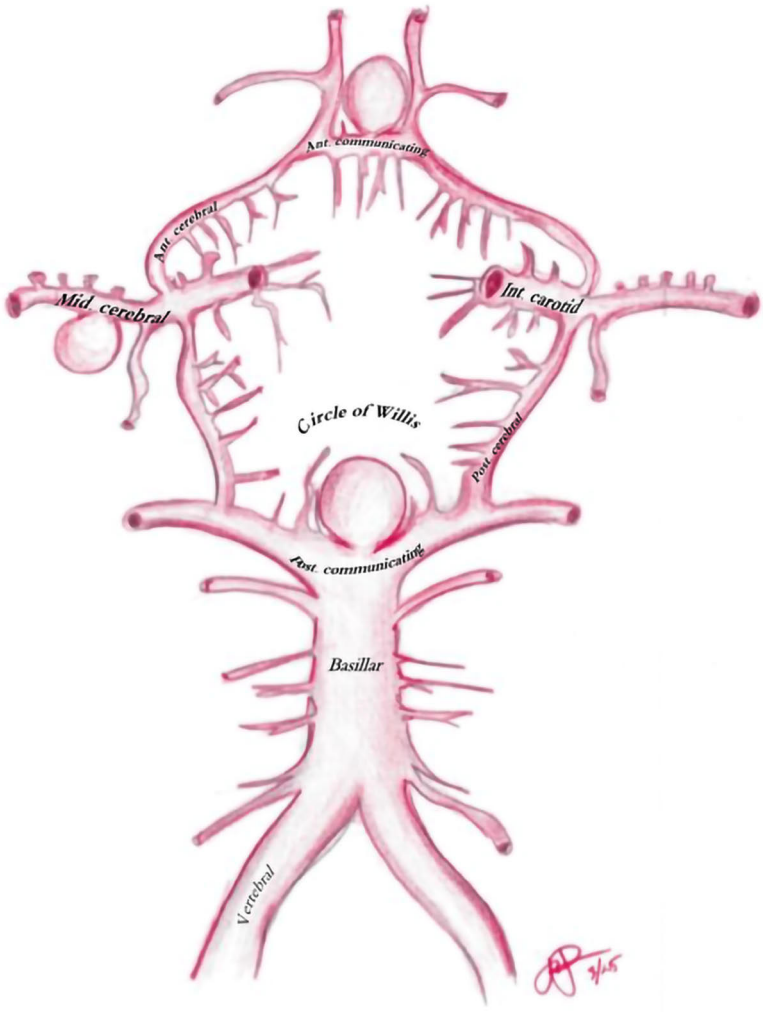


Figure 8. Circle of Willis and the most common locations of ruptured IAs. Rönkkönen 2025.

2.3.1 Epidemiology

The prevalence of IAs is approximately 3% among individuals beyond middle age,[8] and 20%–30% of these individuals have multiple IAs.[166,167] IAs are often asymptomatic and remain undiagnosed until they rupture, leading to aneurysmatic subarachnoid hemorrhage (aSAH), which constitutes a severe medical emergency with significant implications for both mortality and long-term morbidity. Approximately 25% of aSAH patients die before reaching the hospital or the emergency room, and the 1-year case fatality rate approaches 50%, illustrating the severity of this condition.[168,169] Among those who survive the acute phase, only two-thirds are able to return to normal daily activities, and a mere 5% of survivors can resume their pre-aneurysm lifestyle without any limitations or complaints.[170-173]

The increased availability and sensitivity of imaging techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT), has contributed to an increased rate of incidental IA detection.[174] Meanwhile, although the detection of unruptured IAs is increasing, the global incidence of aSAH has been declining. Between 1980 and 2010, the global incidence of aSAH decreased by approximately 40%, declining from 10.2 to 6.1 per 100,000 person-years.[175] However, recent evidence suggests that the incidence of non-traumatic SAH is increasing among the elderly population.[176] Regarding the annual risk of IA rupture, studies have reported rates ranging from 0.5% to 1.4%, depending on various factors such as aneurysm size and location.[177,178] However, when the rupture occurs, it typically affects younger individuals, with a mean age of approximately 50 years, resulting in a significant loss of quality-adjusted life years. Ruptured IAs account for approximately 85% of cases of non-traumatic SAHs, and aSAH constitutes around 2%–5% of all strokes.[175]

2.3.2 Pathophysiology of intracranial aneurysm formation

The pathophysiology of IA is characterized by the interplay of hemodynamic stress, inflammatory processes, extracellular matrix (ECM) degradation, and cellular apoptosis. Hemodynamic forces initiate vessel wall damage, while inflammation and genetic factors facilitate its progression.

Wall shear stress (WSS) is generated by blood flow, which exerts a tangential force on the endothelial lining of the vessel wall. Both increased and decreased WSS inhibit normal endothelial function and are principal initial causes of IA formation.[179-181] At sites where blood flow is turbulent, such as bifurcations and curvatures, WSS has the greatest impact. The Circle of Willis is the most common site of IAs, with round-shape formations, several branches, and bifurcations. A wider bifurcation angle is also associated with the presence of IAs.[182,183] Additionally, the cerebral arteries exhibit a distinctive feature at the apex of bifurcations: a

discontinuity in the medial layer, referred to as the medial gap.[184] These congenital changes and hemodynamic circumstances, along with other risk factors, predispose to aneurysm formation.

Under normal circumstances, ECs produce NO to regulate vascular tone and inhibit inflammation. As a consequence of EC dysfunction, there is a reduction in the production of NO synthase, which in turn leads to the release of a key transcription factor, the pro-inflammatory cytokine nuclear factor kappa-beta (NF-κB). NF-κB controls the expression of leukocyte adhesion molecules (ICAM-1, VCAM-1, E- and P-selectin) and other pro-inflammatory cytokines (TNF-α, IL-1 beta, IL-6). These cytokines not only recruit and activate immune cells but also stimulate those cells to release additional pro-inflammatory cytokines. This positive feedback loop amplifies and sustains the inflammatory response, leading to chronic inflammation within the aneurysmal wall.[185,186]

The presence of WSS and pro-inflammatory cytokines induces the production of a chemokine called monocyte chemoattractant protein-1, which plays a pivotal role in recruiting monocytes into the arterial wall, where they differentiate into macrophages and further contribute to inflammatory processes.[187,188] Macrophages can differentiate into either pro-inflammatory M1 or anti-inflammatory M2 subtypes. M1 macrophages are predominant in the aneurysmal wall, where they release pro-inflammatory cytokines and matrix metalloproteinases (MMPs), contributing to extracellular matrix degradation and the progression of vascular inflammation.[189,190]

Pro-inflammatory cytokines and macrophages stimulate the production and activation of MMP-2 and MMP-3 enzymes, which break down ECM components, including collagen and elastin, crucial for maintaining vessel wall strength and integrity. Furthermore, these occurrences also have an adverse impact on the internal elastic lamina (IEL), leading to its destruction. The disruption of the IEL represents a pivotal phase in the initiation of aneurysm formation.[190]

Pro-inflammatory cytokines, MMP enzymes, WSS, and oxidative stress contribute to VSMC apoptosis, weakening and thinning the arterial wall. During an inflammation process, VSMCs undergo significant pathological transformations, shifting to inflammatory and synthetic phenotypes and losing their contractile function.[186,191]

Active collagen remodeling, regulated by MMPs, is essential for aneurysm formation and expansion. In aneurysmal walls, MMP-2 and MMP-9 degrade elastin and collagen, leading to weakened structural integrity. With diminished elastic fibers, remodeled collagen from transformed VSMCs becomes the primary support. However, collagen has limited distensibility and recoil, contributing to aneurysmal dilation and instability. Excessive MMP activity disrupts the balance between collagen synthesis and degradation, promoting ongoing vessel wall weakening and aneurysm progression.[181,192]

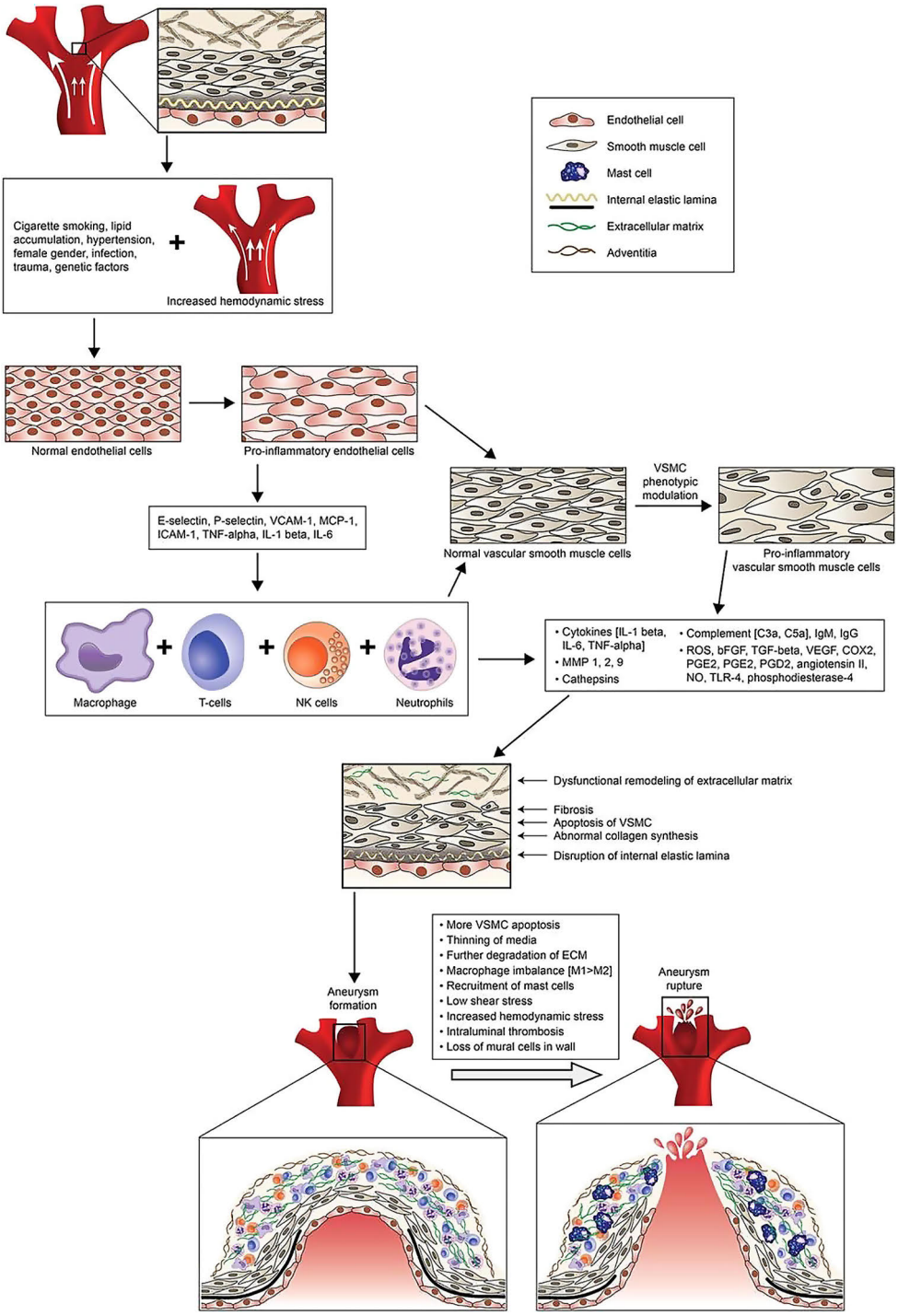


Figure 9. Pathophysiology of IA formation and rupture. Adapted from Chalouhi et al., 2013. ©2013 American Heart Association. Published in Stroke.

2.3.3 Risk factors

2.3.3.1 Non-modifiable

2.3.3.1.1 Gender

There is a gender disparity in the prevalence of IAs. Women have a higher propensity for developing IAs compared to men, a disparity that becomes more pronounced with age. After the age of 50, the prevalence of IAs is twice as high in women as in men.[8,193] Furthermore, IA rupture occurs more often among women than men; 65% of aSAH patients are women,[194] who have a 1.3–1.4-fold greater risk of IA rupture.[171,175,195] After menopause, a decline in estrogen levels occurs, which may contribute to the weakening of arterial wall structures, thereby rendering women more susceptible to IA development and rupture.[196,197]

2.3.3.1.2 Age

The prevalence of IAs is significantly lower among children and young adults, and new IA formations have been documented during follow-up, indicating that IA formation is an age-related phenomenon.[198,199] The prevalence of IA increases with age, with most aneurysms diagnosed in individuals between 40 and 60 years of age. However, in a large meta-analysis, where the age-related prevalence of IAs was adjusted for sex and comorbidities, the increase in IA prevalence in years was no longer significant, suggesting that the observed rise was driven by the accumulation of other risk factors.[8]

2.3.3.1.3 Genetics

A familial history of IAs is a well-established risk factor, with individuals who have a first-degree relative affected by IA exhibiting a higher likelihood of developing aneurysms themselves. Familial clustering of IAs supports the involvement of genetic factors in disease susceptibility. The known common variations of the genome explain 21–29% of the disease.[200] However, it has been estimated that up to 40% of IAs may have a hereditary origin.[201] Approximately 10% of all patients with aSAH have at least one relative with a history of aSAH.[202,203] Furthermore, familial IAs tend to present with an increased risk of rupture and occur at a younger age compared to sporadic cases.[204-206]

In autosomal dominant polycystic kidney disease (ADPKD), pathogenic variants in the PKD1 and PKD2 genes lead to dysfunction in polycystin-1 and polycystin-2 proteins. Polycystin-1 is particularly important as an adhesion molecule in arterial

wall structures, and impaired polycystin production results in a loss of structural integrity.[207] Additionally, ADPKD patients often suffer from systemic hypertension, and the prevalence of IAs in these patients is approximately 10%.[208]

Other monogenic disorders, inherited in a Mendelian pattern, are also associated with increased risk of IAs. These include Ehlers-Danlos syndrome type IV (vascular subtype), Loeys-Dietz syndrome, Marfan syndrome, microcephalic osteodysplastic primordial dwarfism type II, and neurofibromatosis type 1. These conditions are linked to structural abnormalities in the vessel walls, leading to a significantly elevated risk of aneurysm formation.[209,210] However, the presence of these heritable disorders is relatively rare, and their contribution to the overall IA population is limited.

The genetic variations associated with IAs are predominantly expressed in endothelial and mural cells of the Circle of Willis, where they impact both structural and functional components of the arterial wall. These variations contribute to a reduction in arterial wall integrity, increasing the susceptibility to aneurysm formation.[211,212] Genome-wide association studies have identified 17 specific genetic loci on chromosomes associated with the risk of IAs.[200] The genetic variations in these risk loci are typically single nucleotide variants or other regulatory variants, which influence gene function or expression. In addition to common genetic risk variants, rare, high-impact pathogenic variants have been identified, particularly in families with a history of multiple IA cases. These variants contribute to the overall risk of IAs, particularly when combined with other risk factors such as smoking and hypertension.[200,213]

2.3.3.2 Modifiable risk factors

Hypertension and smoking are well-established risk factors for the development, growth, and rupture of IAs.[214-220] The OR for IA associated with smoking is 3.0 (95% CI 2.0–4.4), and 2.9 (95% CI 1.9–4.6) for IA and hypertension. The joint effect of smoking and hypertension significantly increases the risk, with an OR of 8.3 (95% CI 4.5–15.2), indicating a synergistic relationship between these two factors.[221] Among women, the impact of smoking appears even greater (OR 5.8; 95% CI 1.22–11.70) for IA development. When hypertension is also present, the risk escalates substantially, with an OR of 12.6 (95% CI 4.38–36.26).[222] The smoking risk appears to be dose-dependent, with heavy smokers having a higher incidence of aneurysm formation and rupture than light or occasional smokers. Smoking cessation has been shown to reduce this risk significantly.[8,175,223]

In addition to smoking and hypertension, excessive alcohol consumption has been identified as a risk factor for aSAH. This association may be due to alcohol's impact on blood pressure and vascular health.[224] Furthermore, emerging evidence

suggests that insomnia may also increase the risk of both IA and aSAH.[216] Conversely, regular physical activity has been shown to have a protective effect against the risk of aSAH.[225]

Other common CV risk factors, such as hypercholesterolemia, diabetes, and high BMI, have not been consistently linked to an increased risk of IA formation or rupture. Research findings in these areas have been inconclusive, and no definitive evidence has established these factors as significant contributors to the pathophysiology of aneurysms.[216,220,221,224,226,227]

2.3.4 Lipid accumulation and arterial calcification in intracranial aneurysms

The role of arterial calcification in IA remains poorly understood, and its association with generalized atherosclerosis is unclear. Although study findings have been inconsistent, people with atherosclerosis have been observed to have a 1.7 times greater prevalence of UIAs compared to those without the condition.[8]

The accumulation of lipids in the walls of saccular IAs is frequently observed and is suggested to be a principal factor in the degeneration of the wall and risk of rupture. A higher loss of mural cells in the aneurysm wall have been found at sites of lipid accumulation, indicating a more severe degree of degeneration in these areas.[228,229] The ingestion of lipids results in the transformation of VSMCs into foam cells, thereby disrupting their normal physiological functions. Nevertheless, a causal relationship between elevated plasma lipid levels and intra-arterial lipid accumulation has not been proven.[229] It has been suggested that endothelial dysfunction is the cause of lipoprotein accumulation in the arterial wall.[228,230]

In a study conducted by Gade et al. (2019), 65 histological samples of ruptured and unruptured aneurysms were analyzed and the samples were divided into atherosclerotic and non-atherosclerotic groups based on the findings of calcification. Calcification was present in 78% of the samples, with non-atherosclerotic calcifications comprising 76% of all calcifications. Non-atherosclerotic calcifications were found throughout the entire IA wall, rather than limited to the specific layer. However, during IA formation, the elastic laminae are destroyed, and the normal order of arterial wall layers is disrupted, potentially facilitating the wider spread of calcifications. Calcification was more frequently observed in unruptured IAs, and none of the ruptured IA samples exhibited atherosclerotic or macro-calcification.[231]

It has been hypothesized that calcification may stabilize the aneurysm, whereas lipid accumulation in the arterial wall is a risk factor for IA rupture. It is conceivable that the initial atherosclerosis process contributes to arterial wall weakening; however, once calcification has occurred, it appears to offer supportive stabilization to the wall.[232]

2.3.5 Risk characteristics for IA growth and rupture

A significant proportion of IAs remain stable throughout an individual's lifetime. However, some IAs exhibit a propensity for rapid expansion and subsequent rupture.[233] Despite this, the ability to accurately predict which IAs will rupture remains challenging, but certain IA characteristics have been identified as potential risk factors for rupture.

Despite extensive research, a consensus on whether size can accurately define the risk of rupture has not emerged, indicating that the phenomenon behind IA rupture is more diverse than size alone. Some studies suggest that aneurysms larger than 7 mm carry a high risk of rupture,[234,235] whereas several later studies have reported conflicting results, with the majority of ruptured IAs measuring less than 7 mm.[236-238] However, A follow-up study demonstrated that aneurysms with a propensity for growth carried a markedly elevated risk of rupture. Aneurysms that grew during the 2-year follow-up period demonstrated a 12-fold increased risk of rupture.[239] It is estimated that 15%–35% of IAs tend to grow over a 9-year follow-up period.[233]

The risk of IA rupture varies depending on aneurysm location. Arterial wall thickness decreases towards distal arteries, and the rupture risk is greater in smaller arteries where the VSMC layer is thinner. Ruptured IAs are more often located at the apex of bifurcations compared to unruptured ones.[240] It has been observed that ruptured IAs are most commonly located in the anterior circulation (90%), specifically in the middle cerebral artery (32%), anterior (32%) or posterior communicating arteries (14%), and the pericallosal artery (5%).[241] In contradistinction, aneurysms situated in larger arteries, such the cavernous segment of the internal carotid artery, are characterized by a lower propensity for rupture compared to those in other locations.[235] Despite the relative scarcity of IAs in the posterior circulation, those that are present demonstrate a heightened proclivity for growth and rupture. Additionally, these IAs are characteristically smaller in size at the time of rupture.[220,242]

Besides location, the morphology of aneurysms plays a key role in estimating rupture risk. Several parameters have been generated for the purpose of estimating the risk of small aneurysms rupturing. The size ratio, which is the maximum diameter of the IA divided by the vessel lumen, is predictive of rupture risk with a threshold value of 2.3. Another parameter, the aspect ratio (AR), generated by dividing the aneurysm height by the neck width, is associated with a risk of rupture risk when AR>1.5.[243] Aneurysms with a high AR exhibit elongated and narrow-necked shapes, leading to decreased blood flow conditions within the aneurysm sac and a reduction in WSS. This results in an increased inflammatory response within the arterial wall, increasing the risk of rupture.[244] Irregular aneurysm shape has been identified as an independent risk factor for IA growth and rupture.[220,245,246]

Endothelial injury and slower flow within the aneurysm pouch can predispose to thrombus formation along the aneurysm wall. This sustains a chronic inflammatory response, accelerating the degenerative process. The presence of thrombosis is thus both a marker and a driver of the pathological processes leading to aneurysmal instability.[181]

2.3.6 Screening and risk assessment of unruptured intracranial aneurysms

Given the devastating consequences of aSAH, prevention remains the most effective strategy to mitigate poor outcomes, including the screening of IAs and assessing rupture risk. However, balancing follow-up and preventive treatments is difficult due to the significant risk of iatrogenic complications associated with interventions.[247] According to the guidelines for the management of patients with unruptured IAs, screening is recommended for patients with more than one first-degree relative with an IA or aSAH, or for patients with ADPKD and a family history of IA or aSAH.[174]

In a Swedish observational study, patients with one first-degree relative with aSAH had an OR of 2.15 (95% CI 1.77–2.59), whereas individuals with two first-degree relatives showed a markedly increased OR of 51.0 (95% CI 8.56–1117), with a lifetime risk of aSAH reaching up to 20%.[248] In a long-term cohort study, among patients with two or more first-degree relatives with IA or aSAH, IAs were detected in 11% of patients during the initial screening. Continued screening at 5-year intervals revealed de-novo IAs in 5%–8% of cases during follow-up.[249]

According to a systematic review and meta-analysis published in 2015, the prevalence of IAs among patients with ADPKD is approximately 10%. Among ADPKD patients, those with a family history of aSAH or IA were found to have the highest risk of IA compared to other risk factors, with an RR of 2.33 (95% CI 1.60–3.38). Additionally, 23% of ADPKD patients diagnosed with IA had multiple aneurysms.[208]

The PHASES (Population, Hypertension, Age, Size, Earlier subarachnoid hemorrhage, Site) score was developed to estimate 5-year risk of IA rupture.[250] Although it has been validated, it has been shown to underestimate rupture risk, notably in small (<7 mm) aneurysms, and its accuracy in clinical use is poor.[251-253] The PHASES score highlights the impact of aneurysm size while ignoring other structural components. Additionally, it does not take into account smoking or aneurysm multiplicity, both of which are important risk factors for IA and aSAH.[243]

The ELAPSS (Earlier subarachnoid hemorrhage, Location of the aneurysm, Age >60 years, Population, Size of the aneurysm, and Shape of the aneurysm) score estimates the 3- and 5-year risk of IA growth.[254] IA risk factors for growth and rupture are largely similar, and the ELAPSS score incorporates morphological

characteristics more effectively than the PHASES score. However, it faces similar problems: it places too much weight on size, which is the highest-weighted variable in the scale. Validation studies of the ELAPSS score have also shown poor accuracy, with almost half of IAs classified as low to intermediate risk (≤13%–≤19% 5-year risk) still exhibiting growth or rupture.[255,256]

The Unruptured Intracranial Aneurysm Treatment Score (UIATS) was developed by a multidisciplinary team of cerebrovascular experts to support decision-making regarding the management of unruptured intracranial aneurysms. It includes three main domains—patient-related, aneurysm-related, and treatment-related factors—comprising a total of 29 distinct variables, each assigned a weighted score based on its clinical relevance.[257] The application of the UIATS scoring system in clinical practice is overly complex due to the presence of numerous variables. it has also been criticized for being heavily weighed by IA size, underestimating small aneurysms.[258] UIATS has been evaluated retrospectively in a cohort of ruptured IAs, where it recommended treatment in 25% of cases and observation in 32%, resulting in a sensitivity of 44%.[259]

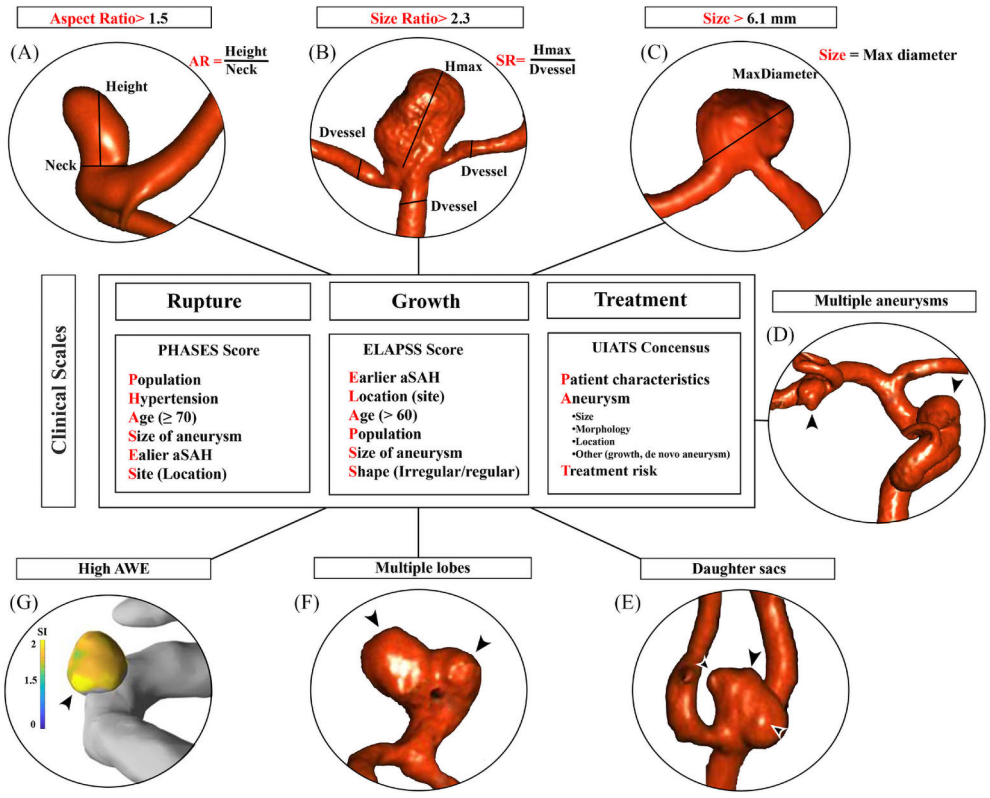


Figure 10. Adapted from Sanchez et al., 2023. ©2023 Elsevier. Published in the Journal of Clinical Neuroscience.

3 Aims

The aim of this thesis was to examine the association between non-invasive lower limb pressure measurements and morbidity, mortality, and the prevalence of intracranial aneurysms.

1. To assess the relationship between different ABI categories and CV as well as all-cause mortality in individuals with ABI values within the normal range (0.9–1.4).
2. To evaluate mortality and morbidity rates in patients with ABI values >1.3 and incompressible ankle arteries. Additionally, to examine the TP in patients with incompressible ankle arteries and its association with mortality.
3. To investigate the role of low ABI and TBI as independent risk factors for the prevalence of IAs.

4 Materials and Methods

4.1 Study cohort and data collection

Turku University Hospital, a tertiary care center in southwest Finland, serves a population of approximately 480,000 residents. The data utilized in all four original publications were derived from a single cohort comprising 2,751 patients who underwent non-invasive peripheral pressure measurements at the hospital's Vascular Laboratory between 2011 and 2013. January 1, 2020, was designated as the study's endpoint. In addition to the non-invasive pressure measurements, age, sex, and underlying diseases were identified from patient records using the International Classification of Diseases (ICD) diagnosis codes. Causes and dates of death were obtained from the Causes of Death Registry of Statistics Finland, which records all deaths of individuals with official permanent residence in Finland.[260]

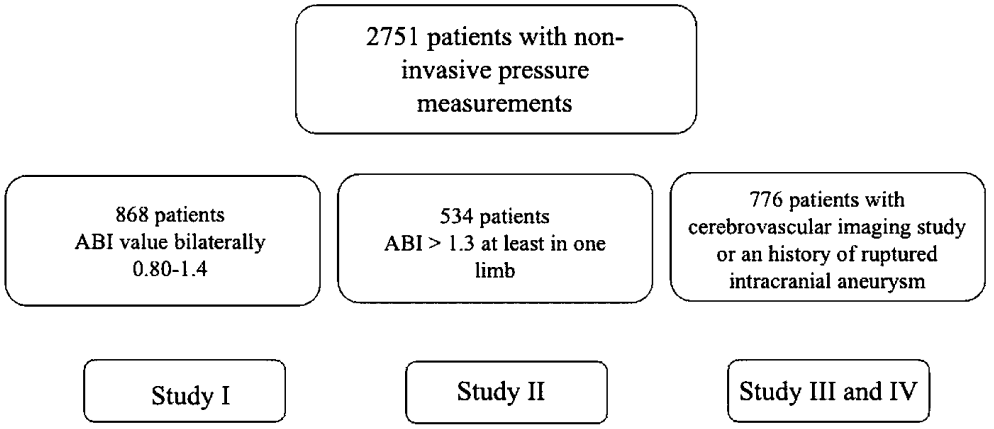


Figure 11. Flow chart of patient distribution across Studies I-IV.

The study cohort underwent a comprehensive review of their history of IAs (Studies III and IV). This entailed a detailed examination of all cerebrovascular imaging studies with the objective of identifying patients who had an IA or a history of treated ruptured IA. Additionally, data on smoking were collected retrospectively

at the time. Current and former smokers were categorized as smokers and patients without a smoking history as non-smokers. Smoking data were obtained through a review of imaging examinations and electronic patient records up to January 1, 2023.

The studies were approved by the Hospital District of South-Western Finland Ethics Committee (IRB number T344/2017). As the studies were retrospective in nature, patient consent was not required.

4.2 ABI, TBI, and TP measurements

A total of 2,751 patients underwent standardized non-invasive peripheral pressure measurements over a 3-year period, from January 1, 2011, to December 31, 2013. To establish a baseline for the study, the first recorded peripheral pressure measurement was defined as the index date for inclusion. The study cohort consisted of patients presenting with various lower limb symptoms not necessarily attributable to PAD. Nonetheless, PAD patients are overrepresented in this cohort compared to the general population, reflecting the clinical context in which these measurements were performed.

All measurements were conducted by trained vascular nurses using the PeriFlux 6000 Laser Doppler device at the Vascular Laboratory of Turku University Hospital. To ensure accuracy, the measurements were performed in a controlled environment, where patients were positioned in a supine position, allowed to rest, and their toes were preheated. The PeriFlux 6000 system includes a localized heating function, which increases the temperature at the measurement site to 40°C, helping to improve detection accuracy, particularly in patients with cold or ischemic feet. This controlled warming reduces variability and ensures more reliable perfusion measurements.

Blood pressure cuffs were placed on both upper arms, ankles, and toes. The cuff on the upper arm was inflated until the blood flow disappeared, then slowly deflated until the Doppler signal returned, marking the brachial SBP. A similar procedure was followed for each ankle, with the Doppler probe positioned over both the posterior tibial and dorsalis pedis arteries. The cuff was inflated until the systolic signal disappeared, up to a pressure of 250 mmHg, and then deflated to determine the SBP for the ankles. If the SBP signal persisted at a level exceeding 250 mmHg, the result was considered incompressible. The ABI for each leg was calculated by dividing the ankle SBP by the brachial SBP.

TP was measured in a similar manner, with the cuff placed around the base of the first toe when possible. If the first toe was absent, the measurement was taken from the nearest subsequent toe. The cuff was inflated until blood flow was cut off and then slowly deflated until the Doppler signal returned, indicating the TP. The TBI was calculated by dividing the toe SBP by the brachial SBP.

4.3 Intracranial aneurysm diagnosis (Studies III and IV)

The entire study cohort (2,751 individuals) was subjected to a comprehensive review for IAs. Of these, 776 patients (28.2%) had available cerebrovascular imaging studies, incorporating both CTA, MRA, or a history of ruptured IAs based on electronic patient records, or imaging signs of treated ruptured IA. All imaging studies were then evaluated by a neurosurgeon, after which each IA imaging finding was closely evaluated by an experienced neuroradiologist to confirm the diagnosis. In cases of discrepancy between the assessments provided by the neurosurgeon and neuroradiologist, a consensus was reached through discussion.

Saccular aneurysms >2 mm in size and located intracranially, as determined by imaging studies, were included in the study. Aneurysms were classified as intra- or extracranial based on Bouthillier's classification. The clinoid segment (C5) served as the reference point: aneurysms located in this segment or further distally were classified as intracranial, while those in the cavernous segment (C4) were considered extracranial and were excluded from the study. Further on, the IAs were classified by location as internal carotid artery (ICA), anterior cerebral artery (ACA), medial cerebral artery (MCA), and posterior circulation. Patients with both ruptured and unruptured IAs were assigned to the ruptured group.

4.4 ABI cohorts and study endpoints in survival studies (Studies I and II)

In the first study, 868 patients (31.6% of the initial cohort) had bilateral ABI values between 0.8 and 1.4 and were included in the study. The patients were further subcategorized according to ABI values as follows: ABI 0.8–0.89 (n=127), ABI 0.90–0.99 (n=159), ABI 1.00–1.09 (n=202), ABI 1.10–1.19 (n=211), ABI 1.20–1.29 (n=143), and ABI 1.30–1.40 (n=26). The ABI range 0.90–0.99 was considered the borderline ABI group and was used as a reference group alongside ABI 0.80–0.89 in the analysis.

In the second study, patients with abnormally high ABI values (>1.3) were included. Of the 2,751 patients, 534 (19.4%) had ABI>1.3 in at least one limb. These patients were further categorized into three subgroups: both limbs with ABI<2.5 but at least one limb with ABI>1.3 (n=155); one limb with ABI≥2.5 (n=169); and both limbs with ABI≥2.5 (n=210). The ABI≥2.5 group represents patients with incompressible ankle arteries, making it impossible to determine absolute ABI values.

In the first study, the primary endpoints were all-cause and CV mortality over the designated follow-up period. In the second study, all-cause mortality served as the primary endpoint during the follow-up period. The follow-up duration was

defined from the date of the initial ABI measurement, considered the index date, and extended through January 1, 2020.

4.5 Intracranial aneurysm patients and peripheral pressure measurements (Studies III and IV)

Of the initial cohort, 776 patients (28.2%) had a cerebrovascular imaging study or a history of ruptured IA available for analysis. The remaining 1,975 patients were excluded from the study due to the unavailability of this data.

The cohort of 776 patients was analyzed in both Studes III and IV. However, the classification of patients differed between the studies depending on the method of peripheral pressure measurement. In Study III, patients were categorized into four groups based on their ABI values: low ABI (≤0.9), borderline ABI (0.91–0.99), normal ABI (1.0–1.4), and abnormally high ABI (>1.4). In contrast, in Study IV, the patients were classified into three groups based on TBI values: low TBI (<0.5), borderline TBI (0.5–0.69), and normal TBI (≥0.7).

Additionally, in both studies, the cohort was divided into three groups based on aneurysm findings: no IA, unruptured IA, and ruptured IA.

The baseline demographic variables were collected from electronic patient records for further comparison. Smoking history, hypertension, CAD, and CKD were considered clinically significant variables in both studies.

4.6 Statistical methods

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, NY, USA) and JMP 16 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $p \leq 0.05$.

In the **first study**, categorical variables were compared using Fisher's exact test, while continuous variables were analyzed with Student's t-test and one-way ANOVA, following verification of normality using the Shapiro–Wilk test.

Unadjusted survival estimates were calculated using Kaplan–Meier survival analysis, and age-adjusted risk assessments were conducted using logistic regression to calculate the OR for each ABI group. Two separate regression model analyses were conducted: in the first, the ABI 0.80–0.89 group served as the reference, and in the second, the borderline ABI 0.9–0.99 group was used as the reference group. Based on a power analysis for survival outcomes, a minimum sample size of 99 per range category was estimated.

In the **second study**, which compared three different abnormally high ABI groups (>1.3), categorical variables were analyzed using the Chi-square test, while continuous variables were assessed with the Kruskal–Wallis test. Unadjusted

survival estimates were calculated using Kaplan–Meier survival analysis, and differences between ABI groups were evaluated using the log-rank test. Additionally, Cox regression analysis was employed to calculate HRs for comparing patients across the three ABI groups, adjusted for age, sex, and significant variables from univariable analyses.

In the **third study**, comparisons between ABI and IA groups were performed using the Kruskal–Wallis test for continuous, non-parametric data, and one-way ANOVA for normally distributed continuous data. Categorical data were analyzed using the Chi-square test. Associations between ABI groups and IA were examined with multinomial logistic regression. In the first model, adjustments were made for age, sex, and clinically relevant variables, while in the second model, significant variables from univariate analysis were added alongside age and sex. Adjusted ORs with 95% confidence intervals (CIs) were reported for associations.

In the **fourth study**, the cut-off for borderline TBI was identified using Youden's J-index, selected as the optimal predictor for IA presence. The J-index was derived from the ROC curve of a binary logistic regression model with TBI as the predictor variable for IA presence. Univariate and multinomial regression analyses were performed in the same manner as in the third study, with results for TBI group associations presented as ORs.

5 Results

5.1 Study I: Borderline ABI is associated with increased all-cause and cardiovascular mortality within the normal ABI range

In this study, the long-term all-cause and CV mortality across different normal-range ABI groups over an 84-month follow-up period was compared. Of the 2,751 patients, 868 individuals (31.6%) with an ABI between 0.8 and 1.4 measured in both limbs were included in the analysis. The lower ABI results were included in the analysis. The cohort was divided into six ABI subgroups: ABI 0.80–0.89 (n=127), ABI 0.90–0.99 (n=159), ABI 1.00–1.09 (n=202), ABI 1.10–1.19 (n=211), ABI 1.20–1.29 (n=143), and ABI 1.30–1.40 (n=26). The ABI 1.30–1.40 group was underpowered for comparative analyses. Table 1 presents the demographic differences across ABI groups.

Table 1. Baseline demographics.

Variable	0.80–0.89	0.90–0.99	1.00–1.09	1.10–1.19	1.20–1.29	1.30–1.40	P-VALUE
	N=127	N=159	N=202	N=211	N=143	N=26	
Age (mean, ±SD)	70.8 (11.8)	68.9 (15.2)	68.11 (13.1)	68.38 (13.5)	64.2 (16.5)	63.9 (15.0)	<0.001
Sex male (%)	79 (62.29)	85 (53.5)	106 (54.5)	120 (66.9)	91 (63.6)	20 (76.9)	0.105
CAD (%)	42 (33.1)	57 (35.8)	60 (29.7)	48 (22.7)	10 (4.7)	8 (30.8)	<0.001
CHF (%)	32 (25.2)	31 (19.5)	28 (13.9)	33 (15.6)	18 (12.6)	6 (23.1)	0.053
HTA (%)	68 (53.5)	89 (56.0)	111 (65.0)	120 (66.9)	69 (48.3)	9 (34.6)	0.238
FA (%)	32 (25.2)	36 (22.6)	47 (23.3)	53 (25.1)	29 (20.3)	7 (26.9)	0.893
CeVD (%)	16 (12.6)	21 (13.2)	21 (10.9)	23 (10.9)	18 (12.6)	4 (15.4)	0.904
DM (%)	43 (33.9)	63 (39.6)	55 (27.2)	68 (42.2)	54 (37.8)	14 (53.8)	0.034
DM I (%)	7 (5.5)	12 (7.5)	14 (6.9)	13 (6.2)	9 (6.3)	3 (11.5)	0.867
DM II (%)	37 (29.1)	50 (31.4)	42 (20.8)	55 (26.1)	45 (31.5)	11 (42.3)	0.065
Dyslipidaemia (%)	35 (27.6)	44 (27.7)	40 (19.8)	38 (18.0)	36 (25.2)	2 (7.7)	0.039
CKD (%)	19 (15.0)	21 (13.2)	22 (10.9)	26 (12.3)	14 (9.6)	4 (15.4)	0.759
COPD (%)	24 (18.9)	22 (13.8)	18 (8.9)	14 (6.6)	6 (4.2)	3 (11.5)	<0.001
Rheumatoid disease (%)	5 (3.9)	9 (5.7)	17 (6.4)	13 (6.2)	14 (9.8)	3 (11.5)	0.302
Varicose Ulcer (%)	11 (8.7)	14 (8.8)	31 (15.3)	26 (12.3)	13 (9.1)	2 (7.7)	0.312
CV death (%)	39 (30.7)	41 (25.8)	41 (25.5)	19 (13.3)	13 (13.3)	3 (11.5)	0.001

CAD, coronary artery disease; CHF, chronic heart failure; HTA, hypertension; FA, atrial fibrillation; CeVD, cerebrovascular disease; DM, diabetes mellitus; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; SD, standard deviation

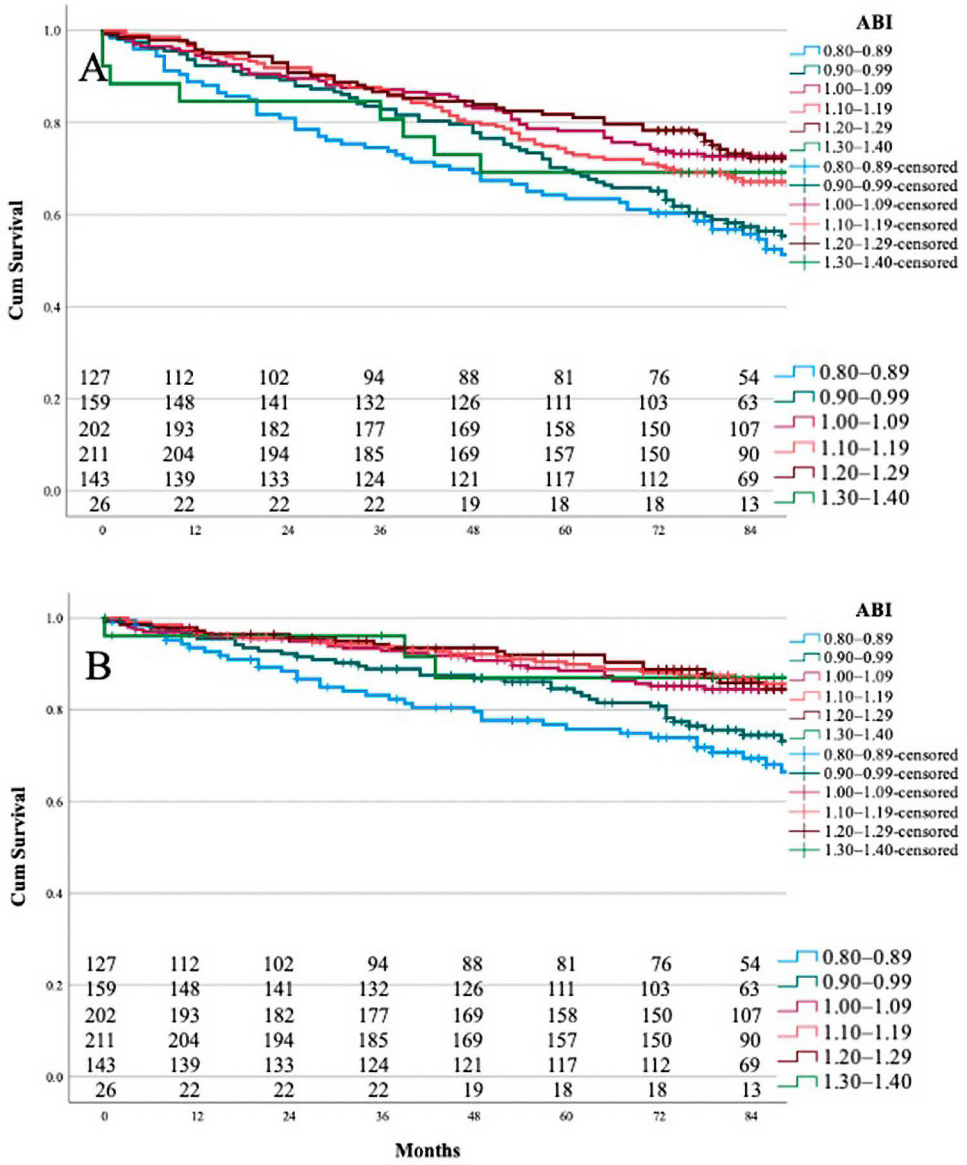


Figure 12. Survival distribution in different ABI groups. Figure A represents overall survival and figure B cardiovascular death-free survival.

Figure 12 illustrates Kaplan-Meier survival curves for each ABI group, detailing overall and cardiovascular death-free survival (CVDFS). When comparing survival times between the ABI groups using the log rank test, no statistically significant differences were observed between the low ABI group (0.80–0.89) and borderline ABI group (0.9–0.99) in terms of overall survival (p=0.393) or CVDFS (p=0.264).

In contrast, significantly longer mean overall survival and CVDFS times were observed in the higher ABI groups (1.0–1.09, 1.10–1.19, 1.20–1.29) compared to the borderline group. A detailed comparison of mean survival times and p-values between ABI groups are presented in Table 2.

Table 2. Mean overall and cardiovascular death-free survival times across ABI groups. Comparisons were made against the borderline ABI group (0.90–0.99) using the log-rank test.

ABI	Mean Survival months ± SE	P-value*	Mean CVDFS months ± SE	P-value*
0.80–0.89	73.0 ± 3.47	0.393	84.2 ± 3.25	0.264
0.90–0.99	78.8 ± 2.76	Reference	90.0 ± 2.49	Reference
1.00–1.09	87.8 ± 2.36	< 0.001	96.2 ± 1.91	0.013
1.10–1.19	85.1 ± 2.28	0.030	97.6 ± 1.77	0.003
1.20–1.29	89.4 ± 2.65	< 0.001	98.0 ± 2.06	0.006
1.30–1.40	80.9 ± 7.97	0.280	96.8 ± 5.57	0.176

ABI, ankle-brachial index; SE, standard error; CVDFS, cardiovascular death-free survival
*Log-rank test P-values

To further examine the association between ABI and mortality, age-adjusted logistic regression analysis was conducted using two different reference groups. In the first model, ABI 0.80–0.89 was used as the reference category, and in the second, the borderline ABI group (0.90–0.99) served as the reference. When using the borderline ABI group (0.90–0.99) as reference, significantly reduced ORs of both overall and CV mortality were observed in ABI categories 1.00–1.29. For overall mortality, ORs ranged from 0.433 to 0.478, and for CV mortality from 0.506 to 0.525. The results were consistent when ABI 0.80–0.89 was used as the reference, indicating an inverse association between ABI values of 1.00–1.29 and mortality risk. The full ORs and p-values from both models are presented side by side in Table 3.

Table 3. Odds ratios for overall and cardiovascular mortality by TBI groups using ABI 0.80-0.89 and 0.90-0.99 as a reference. The multinomial regression models were adjusted for age.

ABI	Overall mortality OR (p-value)	Cardiovascular mortality OR (p-value)
0.80-0.89 ref.		
0.90 - 0.99	0.949 (p = 0.841)	0.856 (p = 0.579)
1.00 - 1.09	0.411 (p < 0.001)	0.442 (p = 0.004)
1.10 - 1.19	0.526 (p = 0.01)	0.348 (p < 0.001)
1.20 - 1.29	0.452 (p = 0.004)	0.449 (p = 0.014)
1.30 - 1.40	0.975 (p = 0.071)	0.383 (p = 0.147)
0.90-0.99 ref.		
0.80-0.89	1.05 (p = 0.841)	1.17 (p = 0.579)
1.00 - 1.09	0.433 (p < 0.001)	0.516 (p = 0.017)
1.10 – 1.19	0.554 (p = 0.011)	0.406 (p = 0.002)
1.20 - 1.29	0.476 (p = 0.005)	0.525 (p = 0.042)
1.30 – 1.40	0.601 (p = 0.283)	0.447 (p = 0.221)

5.2 Study II: Incompressible ankle arteries within the abnormally high ABI range are associated with the highest morbidity and mortality

In this study, the mortality and distribution of various clinical characteristics were examined among patients with abnormally high ABI (>1.3). Of the 2,751 patients who had an ABI greater than 1.3 in at least one limb, 534 (19.4%) met the inclusion criteria and were included in the analysis. These patients were divided into three groups: Group 1 (n=155) included patients with ABI values between 1.3 and 2.5 in at least one limb; group 2 (n=169) included patients with incompressible ankle arteries in one limb; and group 3 (n=210) included patients with incompressible ankle arteries in both limbs. Incompressible ankle arteries were defined as ABI>2.5.

Baseline demographic characteristics were compared across the ABI groups. Compared to group 1, patients in groups 2 and 3 were more likely to be female ($p<0.001$) and older ($p<0.001$) and had higher rates of diabetes ($p=0.013$), CAD ($p=0.001$), heart failure ($p=0.010$), and CKD ($p=0.013$) compared to group 1. The baseline demographic characteristics are presented in Table 4.

Table 4. Baseline demographics by abnormally high ABI groups. ABI >2.5 represents incompressible ankle arteries.

Variable	Group 1 ABI < 2.5 both limbs	Group 2 ABI ≥ 2.5 one limb	Group 3 ABI ≥ 2.5 both limbs	P-value
Age (mean ±SD)	69.7 (12.0)	75.8 (10.6)	74.3 (12.1)	<.001
Female (%)	37 (23.9)	73 (43.2)	84 (40.0)	<.001
Diabetes (%)	74 (47.7)	96 (56.8)	132 (62.9)	0.013
DM I (%)	10 (6.5)	20 (11.8)	22 (10.5)	0.160
DM II (%)	64 (41.3)	77 (45.6)	113 (53.8)	0.056
HTA (%)	99 (63.9)	108 (63.9)	147 (70)	0.332
Hyperlipidemia (%)	40 (25.8)	43 (25.4)	51 (24.3)	0.959
CAD (%)	44 (28.4)	80 (47.3)	86 (41.0)	0.001
CeVD (%)	33 (21.3)	41 (24.3)	44 (21.0)	0.720
CHF (%)	34 (21.9)	62 (36.7)	72 (34.3)	0.010
CKD (%)	25 (16.1)	43 (25.4)	62 (29.5)	0.013
Rheumatic disease (%)	15 (9.7)	22 (13.0)	30 (14.3)	0.424
COPD (%)	12 (7.7)	14 (8.3)	18 (8.6)	0.965
Ulcer (%)	30 (19.4)	27 (16.0)	26 (12.4)	0.234
Malignancy (%)	26 (16.8)	37 (21.9)	53 (25.2)	0.118

DM, diabetes mellitus; HTA, hypertension; CAD, coronary artery disease; CeVD, cerebrovascular disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; SD, standard deviation

In the Kaplan-Meier survival analysis, the mean survival time was 6.2 years (SE = 0.3) in Group 1, and 4.1 years in both group 2 and group 3 ($p < 0.001$). To further evaluate the association between ABI groups and survival, a multivariable Cox regression analysis was conducted. The model was adjusted for age, sex, and significant variables identified in univariate analysis (diabetes, CAD, heart failure, CKD). Group 1 served as the reference category. According to the analysis, group 2 had an HR of 1.6 (95% CI 1.2–2.2, $p = 0.002$) and group 3 had an HR of 1.7 (95% CI 1.2–2.3, $p < 0.001$), indicating a significantly higher risk of death in both groups compared to group 1.

Adjusted survival curves based on the Cox regression model are presented in Figure 13. During the follow-up, overall mortality was significantly lower in group 1 (46.5%) compared to groups 2 (75.1%) and 3 (74.8%) ($p < 0.001$). CV disease was the most common cause of death in all groups, with a higher proportion observed in groups 2 (57.5%) and 3 (59.2%) compared to group 1 (43.1%).

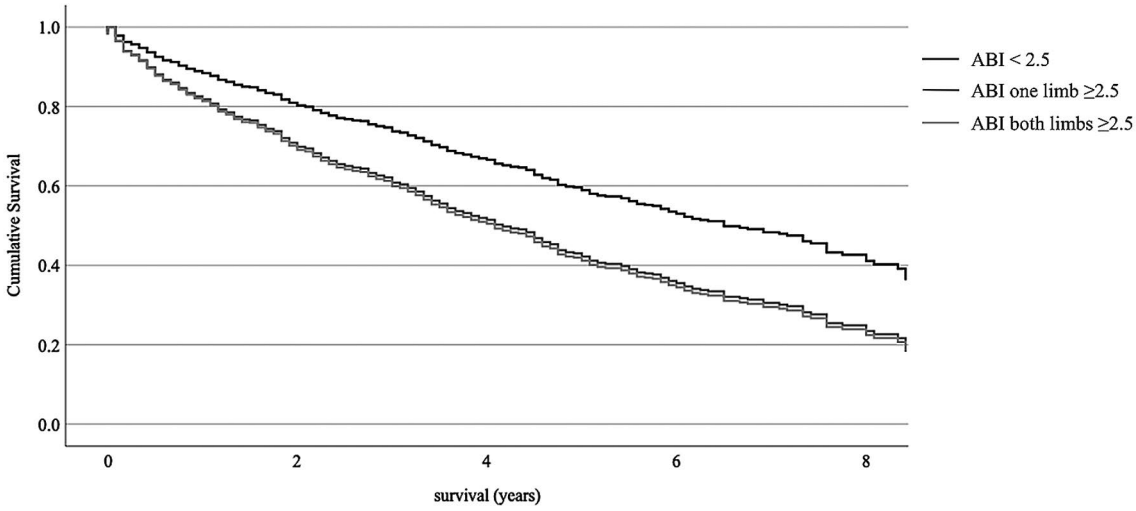


Figure 13. Adjusted Survival in different abnormally high ABI groups.

All patients in group 3 (n=210) had available TP measurements and were further divided into three subgroups based on TP values: TP<30 mmHg (n=35), TP 30–49 mmHg (n=48), and TP≥50 mmHg (n=127). Kaplan-Meier survival analysis and Cox regression analysis were performed for these subgroups as well. The mean survival differed significantly across TP groups (p<0.001), with mean survival times of 2.5 years (SE=0.5) for TP<30 mmHg, 3.6 years (SE=0.4) for TP 30–49 mmHg, and 4.7 years (SE=0.3) for TP≥50 mmHg. Using TP≥50 mmHg as the reference, adjusted HRs were 2.1 (95% CI 1.4–3.2, p<0.001) for the TP<30 mmHg group and 1.4 (95% CI 1.0–2.0, p=0.092) for the TP 30–49 mmHg group. Overall, patients with TP<30 mmHg had a significantly poorer prognosis compared to those with TP≥50 mmHg.

5.3 Study III: Low and borderline ABI is associated with the prevalence of intracranial aneurysms

In the study, the prevalence of IAs across different ABI groups was examined. Of the 2,751 patients in the cohort, 776 (28.2%) were included in the analysis based on the availability of cerebrovascular imaging or a documented history of ruptured IAs. Patients were categorized into four ABI groups: low (≤0.90, n=464), borderline (0.91–0.99, n=47), normal (1.00–1.40, n=208), and high (>1.4, n=57). Based on IA findings, patients were further categorized into three groups: no aneurysm (n=666), unruptured IA (n=97), and ruptured IA (n=13).

A comparison of demographic characteristics among ABI groups is presented in Table 5. Overall, the prevalence of unruptured IAs was 18.1% in the low ABI group,

12.8% in the borderline ABI group, 5.3% in the high ABI group, and 1.9% in the normal ABI group (p<0.001). Besides that, significant differences among ABI groups were found in age (p=0.003), sex (p=0.016), smoking history (p=0.002), diabetes (p<0.001), atrial fibrillation (p=0.008), chronic kidney failure (p<0.001), and COPD (p=0.022). Differences among IA groups were observed in IA multiplicity (p=0.022), smoking history (p=0.013), and median ABI (p<0.001).

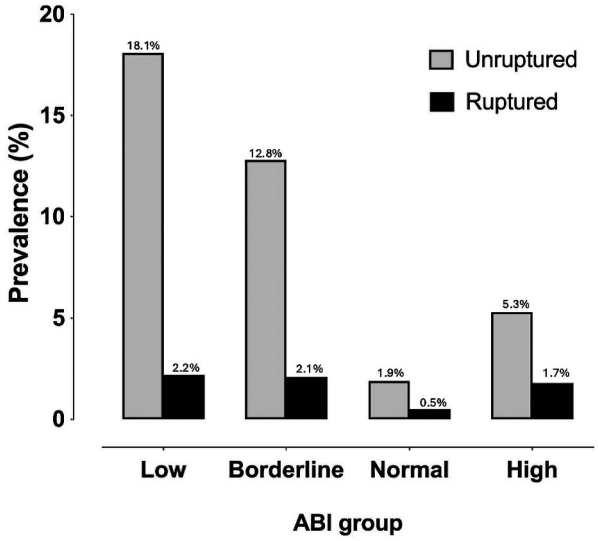


Figure 14. Prevalence of IAs in different ABI groups.

Table 5. Baseline demographics.

Baseline characteristics	Low ABI (≤0.9) n=464	Borderline ABI (0.91–0.99) n=47	Normal ABI (1.0–1.4) n=208	High ABI (>1.4) n=57	p value
Mean age at ABI measurement, y (SD)	69.8 ± 9.6	66.1 ± 13.1	67.0 ± 10.8	68.3 ± 11.5	0.003
Mean age at cerebrovascular imaging, y (SD)	72.2 ± 10.0	68.6 ± 14.2	69.4 ± 11.9	68.0 ± 12.6	0.010
IA screening, n (%)	1 (0.2%)	1 (2.1%)	3 (1.4%)	0 (0%)	0.146
Sex (female), %	38.4%	53.2%	39.4%	22.8%	0.016
Smoking history (yes), %	78.6%	68.9%	55.1%	58.9%	<0.001
Smoking history (missing data), %	6.3%	4.3%	6.7%	8.8%	0.815
Hypertension, %	66.0%	59.6%	60.1%	75.4%	0.129
Diabetes type 1 or 2, %	36.9%	46.8%	35.1%	63.2%	<0.001
Diabetes type 1, %	3.9%	19.2%	7.2%	15.8%	<0.001
Diabetes type 2, %	33.3%	25.5%	27.9%	50.9%	0.008
Hypercholesterolemia, %	30.5%	27.7%	24.0%	36.8%	0.190
Coronary artery disease, %	36.0%	34.0%	29.8%	42.1%	0.270
Chronic heart failure, %	16.4%	21.3%	13.9%	28.1%	0.069
Atrial fibrillation, %	19.4%	29.8%	26.0%	36.8%	0.008
Chronic kidney failure, %	11.9%	19.2%	10.6%	33.3%	<0.001
Chronic obstructive pulmonary disease, %	14.7%	12.8%	6.3%	14.0%	0.022
Rheumatoid disease, %	7.3%	6.4%	11.1%	10.5%	0.371
Varicose ulcer, %	5.6%	8.5%	7.2%	14.0%	0.112
Malignancy, %	19.4%	12.8%	17.8%	31.6%	0.070
Prevalence of IAs, % (n)	20.3% (94)	14.9% (7)	2.4% (5)	7.0% (4)	<0.001
Unruptured IAs, % (n)	18.1% (84)	12.8% (6)	1.9% (4)	5.3% (3)	<0.001
Ruptured IAs, % (n)	2.2% (10)	2.1% (1)	0.5% (1)	(1.7%) (1)	0.277

Multinomial regression analysis (Table 6) was performed to estimate the association between ABI levels and unruptured IA presence. In the first model, clinically significant variables were included along with age and sex. Statistically significant ORs were observed for low ABI (OR 13.2, 95% CI 4.01–42.24, p<0.001), borderline ABI (OR 8.68, 95% CI 2.05–36.69, p=0.003), and smoking history (OR 2.01, 95% CI 1.07–3.77, p=0.030). In a second model that included variables significant in univariate analysis (including smoking history), results were consistent: the OR for low ABI was 12.69 (95% CI 3.91–41.12, p<0.001), for borderline ABI 8.80 (95% CI 2.09–36.98, p=0.003), and for smoking history 1.97 (95% CI 1.05–3.86, p=0.035).

Table 6. Odds ratios for intracranial aneurysms by ABI group and risk factors. The first multinomial regression model was adjusted for age, sex, and clinically relevant risk factors. The second model was adjusted for age, sex, and statistically significant variables in univariate analysis.

	OR	95 % CI	P-value
Model 1			
Age	1.02	0.99–1.04	0.209
Sex (female)	1.53	0.95–2.46	0.083
Hypertension	1.23	0.75–2.02	0.417
Coronary artery disease	0.61	0.37–1.02	0.058
Smoking history	2.01	1.07–3.77	0.030
Chronic kidney disease	1.46	0.74–2.84	0.273
Ref. ABI 0.9–1.4			
Low ABI ≤ 0.9	13.02	4.01–42.24	<0.001
Borderline ABI 0.9–1.0	8.68	2.05–36.69	0.003
High ABI > 1.4	3.97	0.76–20.76	0.103
Model 2			
Age	1.01	0.99–1.04	0.295
Sex (female)	1.58	0.99–2.54	0.056
Smoking history	1.97	1.05–3.68	0.035
Ref. ABI 0.9–1.4			
Low ABI ≤ 0.9	12.69	3.91–41.12	<0.001
Borderline ABI 0.9–1.0	8.80	2.09–36.98	0.003
High ABI > 1.4	4.27	0.83–22.00	0.083

5.4 Study IV: Low TBI is associated with the prevalence of intracranial aneurysms

In the study, the association between TBI values and the prevalence of IAs was assessed. Of the 2,751 patients in the cohort, 776 were included in the analysis based on the availability of TBI measurements, cerebrovascular imaging, or a documented history of ruptured IAs. To determine the optimal cut-off for low TBI, we used Youden's J-index as a predictor for IA presence. The analysis identified a cut-off value of 0.5, which was used to create three groups: low TBI (<0.5, n=473), borderline TBI (0.5–0.69, n=180) and normal TBI (≥0.7, n=123). Additionally, patients were categorized by IA status: no aneurysm (n=666), unruptured aneurysm (n=97), and ruptured aneurysm (n=13).

Baseline demographic and clinical characteristics across TBI groups are presented in Table 7. A significant difference of prevalence of IAs was found across the TBI groups: The prevalence of unruptured IAs was 16.3% in the low TBI group, 8.3% in the borderline TBI group, and 4.1% in the normal TBI group ($p<0.001$). Also, significant differences between TBI groups were found in hypertension ($p=0.032$), type II diabetes ($p=0.037$), CAD ($p=0.025$), and smoking history ($p=0.003$). Statistically significant differences across IA groups were found in smoking history ($p=0.003$), and the mean TBI was significantly lower in patients with unruptured or ruptured IAs than in those without aneurysms ($p<0.001$)

Table 7. Baseline demographics.

	TBI < 0.5 (n=473)	TBI 0.5–0.69 (n=180)	TBI ≥ 0.7 (n=123)	P-value
Mean age at TBI measurement, years, ±SD	70.2 ± 9.6	67.9 ± 13.8	64.2 ± 14.1	<0.001
Sex (female) %	37.8	40.6	37.4	0.792
Hypertension %	68.3	58.9	59.3	0.032
Diabetes all %	40.9	38.9	31.7	0.177
DM type I %	6.8	4.4	8.9	0.289
DM type II %	34.1	35.6	22.8	0.037
Hypercholesterolemia %	31.1	26.3	25.2	0.278
Coronary artery disease %	38.3	30.6	26.8	0.025
Chronic heart failure %	18.0	15.0	15.4	0.596
Atrial fibrillation %	22.2	24.4	24.4	0.773
Chronic kidney disease %	13.8	15.0	10.6	0.528
Smoking history %	74.7	62.0	63.7	0.003
Smoking data missing %	6.6	5.0	8.1	0.545
Rheumatoid disease %	8.5	8.9	8.1	0.972
Malignancy %	19.7	20.6	17.1	0.742
IA % (n)	17.8 (84)	9.4 (17)	7.3 (9)	0.001
Unruptured IA % (n)	16.3 (77)	8.3 (15)	4.1 (5)	<0.001
Ruptured IA % (n)	1.5 (7)	1.1 (2)	3.3 (4)	0.307

Multivariable regression analysis (Table 8) adjusted for age, sex and clinically significant variables showed a significant association between unruptured IAs and low TBI (OR 3.75, 95% CI 1.49–9.708, p=0.006), history of smoking (OR 2.59, 95% CI 1.408–4.762, p=0.002), and female sex (OR 1.63, 95% CI 1.026–2.604, p=0.039) compared to normal TBI values. The OR for borderline TBI was also increased, but did not show statistical significance (OR 1.80, 95% CI 0.623–5.220, p=0.277). In the second model, a multinominal regression analysis adjusted for sex, age, and smoking history (significant in univariate analysis) showed that low TBI remained the strongest independent predictor of IA prevalence (OR 3.59, 95% CI 1.393–9.272,

p=0.008). Similarly, a history of smoking (OR 2.558, 95% CI 1.393–4.695, p=0.002) and female sex (OR 1.68, 95% CI 1.059–2.673, p=0.027) also remained significant predictors, although with lower ORs compared to low TBI.

Table 8. Odds ratios for intracranial aneurysms by TBI group and risk factors. The first multinomial regression model was adjusted for age, sex, and clinically relevant risk factors. The second model was adjusted for age, sex, and statistically significant variables in univariate analysis.

	OR	95% CI	P-value
Model 1			
Age	1.020	0.995–1.045	0.118
Sex (female)	1.634	1.026–2.604	0.039
Hypertension	1.183	0.723–1.932	0.504
Coronary artery disease	0.612	0.371–1.011	0.055
Smoking history	2.591	1.408–4.762	0.002
Chronic kidney disease	1.387	0.722–2.667	0.326
Ref. TBI ≥ 0.7			
TBI 0–0.49	3.749	1.448–9.708	0.006
TBI 0.5–0.69	1.803	0.623–5.220	0.277
Model 2			
Age	1.017	0.993–1.042	0.172
Sex (female)	1.683	1.059–2.673	0.027
Smoking	2.558	1.393–4.695	0.002
Ref. TBI ≥ 0.7			
TBI 0–0.49	3.593	1.393–9.272	0.008
TBI 0.5–0.69	1.777	0.615–5.129	0.288

6 Discussion

PAD is strongly associated with coexisting CAD and CeVD, with patients suffering from PAD exhibiting the highest incidence of MACE compared to other CVDs. This underscores the systemic nature of PAD and highlights the critical need for comprehensive CV risk assessment in these patients. Despite the presence of numerous international guidelines advocating for the use of secondary prevention pharmacotherapy and the rigorous management of modifiable risk factors, the real-world implementation of these recommendations remains suboptimal.[261] Moreover, PAD is frequently underdiagnosed and undertreated compared to other CVDs.

The predictive value of the ABI in CV risk assessment has been extensively validated across numerous studies. It can be regarded as a biomarker of CV risk, demonstrating prognostic utility that exceeds that of traditional risk factors when evaluated independently, while also highlighting its simplicity, accessibility, and affordability.[262] However, to maintain the precision and reliability of the measurement, it is crucial that the assessment is conducted under rigorously controlled and standardized conditions. The ABI could be described as a biomarker of CV risk; the prognostic information is greater than any other risk factor alone.

The TBI and TP are more commonly utilized in clinical practice to assess tissue viability and predict wound healing. However, emerging evidence suggests that these measures also possess prognostic value in estimating CV risk, similar to the ABI.[162] Nevertheless, their role in CV risk stratification remains significantly less studied and warrants further research.

6.1 Study I: Borderline ABI and its association with mortality

Borderline ABI (0.9–0.99) is often considered a gray zone, where individuals do not meet the clinical criteria for PAD but may still exhibit a greater burden of subclinical atherosclerosis compared to those with normal ABI values.[263] One of the primary concerns with borderline ABI is its potential to underestimate vascular disease, potentially leading to missed opportunities for timely implementation of lifestyle modifications and medical interventions. A borderline ABI has been associated with increased MACE and all-cause mortality, and individuals with a borderline ABI

often present with a broader range of CV risk factors, reinforcing its potential as a prognostic marker.[143]

Study I demonstrated that individuals with a borderline ABI (0.90–0.99) had significantly lower survival rates for both CV and all-cause mortality compared to those with ABI values between 1.00 and 1.29. This finding highlights that even minor deviations from the optimal ABI range may carry prognostic significance. Notably, 21% of individuals who were previously categorized as having a normal ABI were reclassified into the borderline ABI group, where CV mortality was 10% higher than in those with an ABI of 1.0–1.3. In previous studies, 6.8–13.4% of individuals with an initially normal ABI (0.9–1.4) were later reclassified as having a borderline ABI, whereas in our study, the proportion was slightly higher.[143,263-266] Furthermore, patients in the borderline ABI group exhibited a higher prevalence of CAD and COPD, both of which are strongly associated with a smoking history and an increased risk of generalized atherosclerosis. Although MAC is known to cause falsely elevated ABI values, it does not necessarily lead to abnormally high (ABI>1.4) results; rather, it may raise ABI into the borderline or normal range. Nevertheless, in our study, risk factors commonly associated with MAC, such as CKD and diabetes, were not overrepresented in the borderline ABI group. Therefore, the masking effect of MAC is unlikely to account for the elevated mortality observed in this group.

A key aspect of the Study I design was that all participants had ABI values within the 0.8–1.4 range in both limbs**,** suggesting that the study population was relatively healthy in terms of vascular health. Given this, an age-adjusted logistic regression model was employed, which confirmed that a borderline ABI remained significantly associated with both all-cause and CV mortality.

An unexpected finding in Study I was that mortality rates were similar between individuals with an ABI of 0.80–0.89 (mild PAD) and those with borderline ABI (0.90–0.99). This challenges the traditional classification of borderline ABI as a lower-risk category, instead suggesting that these individuals may carry a CV risk comparable to those with mild PAD. Such findings align with growing evidence that a borderline ABI is linked to significant subclinical CV risk.

Studies have shown that individuals with borderline ABI exhibit higher levels of endothelial dysfunction,[267] a well-established precursor of atherosclerosis and a contributing factor to CV events. Additionally, borderline ABI has been linked to an increased risk of developing heart failure,[264] further emphasizing its role as an early indicator of CV diseases. It has also been observed that patients with borderline ABI are at an increased risk of developing lower ABI values over time, indicating disease progression and potential deterioration of arterial function.[144] These findings challenge conventional ABI cut-off values and reinforce the importance of ABI as a marker of systemic atherosclerosis and overall CV risk burden.

6.2 Study II: Incompressible ankle arteries and prognosis

The association between an abnormally high ABI and mortality remains a subject of ongoing debate, with conflicting findings across studies. The predictive value of diabetes in relation to elevated ABI has also been widely discussed. Some studies have reported increased CV mortality among individuals with a high ABI, regardless of diabetes status, while others suggest that elevated mortality is observed only in diabetic patients with a high ABI.[153,161] Conversely, certain studies, particularly those including relatively healthy individuals, have found no significant association between elevated ABI and increased mortality.[268]

The findings of Study II demonstrated that patients with incompressible ankle arteries in at least one lower limb exhibited poorer overall survival and higher CV mortality compared to those with elevated but compressible ankle arteries. Furthermore, patients with incompressible arteries had a greater burden of comorbidities, including a higher prevalence of CAD, diabetes, chronic heart failure, and CKD**,** in addition to being older and more frequently female. These results underscore the clinical significance of ankle artery compressibility, as decreasing compressibility seems to be associated with increased mortality and morbidity. Notably, in the Strong Heart Study, where high ABI was linked to greater all-cause mortality than low ABI, many of the elevated ABI values were, in fact, incompressible, which may have contributed to the observed increase in mortality rate.[150] Importantly, in Study II, the survival analysis was adjusted for key confounding variables, including age, sex, diabetes, CAD, chronic heart failure, and CKD. Despite these adjustments, incompressible arteries remained significantly associated with mortality, suggesting that traditional CV risk factors alone do not fully account for the increased risk. These findings indicate the presence of additional mechanisms contributing to the elevated mortality risk in patients with incompressible arteries.

The underlying pathophysiological mechanisms linking elevated ABI to increased CV risk remain incompletely understood. A widely accepted hypothesis suggests that elevated ABI results from vascular stiffening due to MAC, a concept reflected in current clinical guidelines.[142] However, evidence supporting the notion that high ABI is solely due to MAC in peripheral arteries remains limited. Only four studies have explicitly examined this relationship.[52,269-271] These studies confirmed an association between MAC and elevated ABI, with affected individuals being older, more often male, more likely diabetic, and less likely to smoke—a demographic profile consistent with established MAC characteristics. However, the diagnostic accuracy of ABI for detecting MAC is poor, with low sensitivity (15.7%) despite high specificity (94%). As ABI values increased, the association with MAC strengthened, further supporting the idea of that there can be a linear association

between the severity of MAC and ABI results.[269] Altogether, elevated ABI alone is not a reliable marker for MAC, but MAC can contribute to an increased ABI.

Several alternative explanations for elevated ABI values have been proposed. In healthy individuals with an elastic aorta and non-obstructive peripheral arteries, pulse pressure amplification contributes to increased pressure as the pulse wave propagates through the arterial tree. This physiological phenomenon leads to higher ABI values, reflecting vascular elasticity and wave reflection dynamics, and represents a normal hemodynamic response to vascular function.[272,273] Additionally, factors beyond MAC can contribute to arterial stiffening, leading to similar ABI elevations but through distinct pathophysiological mechanisms.[274] Measurement-related factors may also influence ABI results. Improper cuff size, particularly in individuals with obesity or edema, can lead to artificially elevated ABI values by interfering with proper arterial compression during measurement. Likewise, higher muscle mass in the lower extremities has been positively associated with ABI in the general population, further complicating the interpretation of elevated ABI values.[275]

While multiple factors may contribute to elevated ABI, the excess mortality observed in individuals with a high ABI is likely primarily driven by MAC-related vascular changes. MAC induces arterial stiffening, impairing the ability of blood vessels to buffer the pulsatile cardiac output. This increased arterial rigidity leads to higher systolic blood pressure, increased left ventricular workload, and subsequent hypertrophy, all of which elevate the risk for CV events.[47]

The degree of ankle artery compressibility likely serves as a key indicator of MAC severity and is thus linked to CVD risk. As tibial artery compressibility declines, the probability of MAC increases, correlating with greater CVD risk. Conversely, among patients with only slightly elevated ABI values, the proportion of healthy individuals with physiologically elevated ABI is likely higher. Additionally, while it is plausible that mechanisms other than MAC are unlikely to cause arterial incompressibility, the degree to which this is true remains uncertain. Moreover, the findings from Study II indicate that CKD, diabetes, and advanced age were more prevalent among individuals with incompressible arteries, aligning with the well-established risk profile of MAC.

Additionally, incompressible arteries resulting from MAC may obscure the presence of clinically significant atherosclerosis, potentially leading to an underestimation of CVD risk. In Study II, 40% of patients with bilateral incompressible ankle arteries had a TP below 50 mmHg, indicating that a substantial proportion of individuals with incompressible ankle arteries also have PAD.

6.3 Studies III and IV: Decreased pressure measurements and intracranial aneurysms

Studies III and IV revealed a significant association between low or borderline ABI, low TBI, and IAs. The prevalence of unruptured IAs was 18.1% in the low ABI group**,** 12.8% in the borderline ABI group**,** and 16.3% in the low TBI group. These findings suggest that decreased pressure measurements may serve as indicator of an increased risk of IA, potentially through shared vascular pathophysiology.

Both ABI and TBI are strong markers of generalized atherosclerosis, raising the question of its role in IA pathophysiology. Arterial calcification is frequently observed in IAs, as demonstrated by a recent study in which 78% of IA samples contained calcification within the aneurysm wall.[231] Additionally, a large Finnish cohort study found that patients with IAs had a significantly higher abdominal aortic calcification index—a measure of systemic calcification—compared to patients without IAs. This study also demonstrated that greater arterial calcification was associated with an increased risk of aneurysm rupture, suggesting that vascular calcification plays an important role in IA progression.[276]

The pathophysiological relationship between atherosclerosis and IAs is not understood, and the precise role of calcification in IA formation remains unclear. However, both conditions share common mechanisms involving endothelial dysfunction and chronic inflammation. Hemodynamic stress is another key factor, promoting arterial wall degeneration and increasing the likelihood of aneurysm formation and atherosclerosis. Histological studies of aneurysmal arterial walls frequently reveal both arterial calcification and inflammation, suggesting that atherosclerosis may contribute to vascular wall weakening, ultimately predisposing individuals to aneurysm development.

Established CV risk factors, including smoking and hypertension, are shared by IAs and decreased pressure measurements. However, in Studies III and IV, the association between smoking and hypertension with IAs was significantly weaker compared to low/borderline ABI or low TBI, suggesting that an alternative mechanism may be responsible for this relationship. Beyond traditional CV risk factors, low ABI is also observed in individuals without these risk factors, suggesting that additional mechanism may contribute to its association with IAs.[277] In addition, a correlation has been established between low ABI and elevated non-cardiovascular mortality rates, indicating its relevance as a broader indicator of systemic health decline rather than being exclusively tied to CVDs.[278]

While low ABI and TBI are markers of systemic atherosclerosis and increased CVD risk, they do not represent identical populations, as their risk factor profiles differ. The relationship between ABI and TBI is not linear, reflecting distinct vascular pathophysiology and patient characteristics. Generally, lower ABI values tend to correlate with lower TBI values, whereas TBI scores demonstrate greater

variability among individuals with higher ABI levels.[161] Our study was unable to assess this relationship, as ABI and TBI values were documented based on the highest and lowest values rather than per limb side. This variability in TBI results among those with elevated ABI results is likely influenced by MAC, which can artificially elevate ABI values while leaving TBI results unaffected. This is particularly relevant for diabetics, who often exhibit higher ABI values due to MAC despite having significant vascular disease. Patients with a normal or elevated ABI but low TBI may have either a distal arterial occlusion, or a significant proximal occlusion masked by MAC. In fact, patients with an elevated ABI and low TBI have the worst prognosis.[147] This suggests that both measurements reflect different but clinically significant vascular pathologies, reinforcing the importance of assessing TBI alongside ABI to better characterize an individual's overall risk profile.

In Study III, diabetes prevalence was significantly higher in the high ABI group compared to the low or normal ABI group, while it was also more common in lower TBI groups than in the normal TBI group, reflecting the phenomenon described earlier. When comparing other risk factors between the low ABI and low TBI groups, there were no significant differences in age (69.2 vs. 70.2 years) or gender distribution. However, smoking history was slightly more prevalent in the low ABI group (78%) than in the low TBI group (74.7%). Conversely, diabetes was more frequent in the low TBI group (40.9%) compared to the low ABI group (36.9%). Hypertension was present in 66% of individuals in the low ABI group and 68% in the low TBI group. Overall, the most notable differences were observed in smoking and diabetes prevalence, while other risk factors remained largely comparable between the two groups. Diabetes has not been linked to the formation of IA, whereas smoking and hypertension are well-established risk factors. The higher prevalence of diabetes and the lower prevalence of smoking in the low TBI group compared to the low ABI group highlight differences in risk factor distribution between these measurement techniques and may partially contribute to the variation in IA prevalence between the groups. However, the extent to which these differences explain the observed prevalence of intracranial aneurysms in low ABI versus low TBI groups remains uncertain and warrants further investigation.

Although the precise mechanism linking low ABI and TBI values to the prevalence of IAs remains unclear, the findings of these studies suggest that the risk factor profile of IA patients is broader than previously recognized. The significant association between decreased pressure measurements and IA prevalence indicates that CV risk factors may play a more crucial role in IA development than previously thought. These findings support the need for a more comprehensive approach to IA risk assessment, incorporating markers of systemic atherosclerosis and arterial stiffness alongside traditional risk factors.

Given the accessibility and non-invasive nature of ABI and TBI measurements, they could serve as valuable screening methods for identifying individuals who may benefit from further imaging screening for IAs. The current risk stratification models, such as PHASES and ELAPSS scores, are designed to estimate the risk of rupture or growth of already identified IAs and thus do not assist in IA screening. The findings of the present studies support the potential utility of peripheral pressure measurements as a screening marker in IA screening, particularly in patients with elevated CV risk. Incorporating peripheral pressure measurements into clinical decision-making could improve early detection strategies by guiding more targeted screening efforts in at-risk populations.

Finally, based on the study findings, there is a significant association between IAs and elevated CV risk. To optimize patient outcomes in cases of IAs, a comprehensive, dual-focused clinical approach is warranted. This entails not only direct management of the IAs themselves but also a concerted effort to mitigate CV mortality. By integrating aneurysm-specific treatments with strategies to reduce CV risk, clinicians can improve overall patient prognosis and long-term survival.

6.4 Limitations

This study has several limitations that need to be acknowledged. First, the data were retrospectively collected, which inherently limits the ability to control for potential confounders and standardize data collection procedures. Second, the study was conducted at a single center, which may limit the generalizability of the results to broader populations. Additionally, the cohort consisted of patients who underwent peripheral pressure measurements due to lower limb symptoms, meaning that the findings are not directly applicable to the general population. Since these patients were already experiencing potential vascular symptoms, there is a possibility that the study population included a higher proportion of individuals with PAD compared to the general population, potentially influencing the observed associations with endpoints.

Another important limitation concerns the availability of cerebrovascular imaging data in Studies III and IV. Of the original study cohort (2751), only 28.2% had imaging studies available for analysis, and among those, IAs were identified in just 110 patients. Although the observed associations were statistically significant, the relatively small final study population limits the generalizability of the findings.

A further limitation relates to the reliability and completeness of smoking data. Studies I and II did not include smoking data, leaving its potential impact on the study results unexamined. Additionally, in Studies III and IV, the available smoking records did not consistently differentiate between current and former smokers, making it impossible to assess the independent impact of active smoking on the study

outcomes. Given that smoking is a well-established risk factor for both PAD and IAs, the inability to accurately classify smoking status may have introduced residual confounding into the analyses.

Furthermore, in Studies III and IV, only the lowest ABI and TBI values from the most affected limb were used in the analyses. While this approach ensures that the most severe impairment is captured, it does not provide information on potential overall vascular burden.

6.5 Future aspects

Patients with symptomatic PAD are typically prescribed antithrombotic therapy as an essential component of secondary prevention. As has been repeatedly established, patients with a low ABI, regardless of symptomatic status, face an increased risk of MACE. However, while antithrombotic therapy has been shown to significantly reduce CV events in symptomatic PAD patients, its benefits in asymptomatic PAD patients remain unproven. Notably, clinical trials comparing aspirin to placebo in asymptomatic PAD patients have often included individuals with relatively high ABI values. This likely influenced the results, as the CV risk in this subgroup may have been lower than that observed in more severe PAD cases.[279,280]

It is also important to acknowledge that patients with asymptomatic PAD may experience mobility limitations that mask lower extremity symptoms, or they may present with atypical symptoms that are not readily attributed to PAD. Although MACE events are more frequent in symptomatic PAD patients, the difference remains significant even when comparing asymptomatic PAD patients to those without PAD.[262] Given the frequent coexistence of PAD with CAD or CeVD, many patients with PAD already have an independent indication for antithrombotic therapy. Nevertheless, the question has been raised as to whether antithrombotic therapy is indicated in patients with reduced ABI, even in the absence of overt symptoms. Antiplatelet therapy exerts its primary effect through platelet aggregation inhibition, but it also has recognized anti-inflammatory properties. Inflammation plays a key role in the pathophysiology of both PAD and IA. Emerging evidence suggests that ASA may mitigate IA growth and rupture risk.[281] A randomized controlled trial is currently investigating this hypothesis, which may further inform the potential benefits of antithrombotic therapy beyond conventional CV indications.[282]

Given the strong prognostic implications of ABI, an important consideration is whether incorporating ABI measurement as a routine component of preventive health screenings may be warranted. ABI is a simple, non-invasive, and cost-effective diagnostic method that can identify subclinical atherosclerosis and stratify CV risk. Despite its clinical utility, ABI screening is not systematically incorporated

into general health assessments. If routine ABI screening were implemented, it could facilitate early identification of high-risk individuals, allowing for timely initiation of preventive strategies, including lifestyle interventions and pharmacotherapy.

Several key directions for future research arise from the findings of the studies in this thesis. First, the association between MAC and elevated ABI warrants further investigation, particularly regarding its impact on mortality. It would be interesting to examine the association between the degree of MAC in the lower limbs and elevated ABI values, specifically whether the degree of MAC is linearly associated with elevated ABI and how this, in turn, relates to mortality. A deeper understanding of the role of MAC in ABI elevation and its prognostic implications could enhance risk stratification and inform clinical decision-making for patients with high ABI values. This research could help clarify whether elevated ABI primarily reflects MAC and guides appropriate management strategies for affected individuals. In addition, the development of non-invasive diagnostic tools to help clinicians differentiate whether PAD in each patient is driven by atherosclerosis, MAC, or a combination of both would be highly beneficial. Such advancements could enable more precise therapeutic targeting to maximize patient outcomes.

Second, there is a need to establish more precise threshold values for TBI using imaging studies and ABI results as reference standards. Defining optimal cut-off values could improve the diagnostic accuracy of TBI, enhance its clinical utility in detecting PAD, and strengthen its role as a prognostic marker for CV risk assessment. Further research into the distinct molecular pathways underlying MAC may also provide valuable insights, potentially identifying novel therapeutic targets that could aid in the development of new treatments aimed at mitigating its effects.

The association between arterial calcification and IAs necessitates further investigation. Given the observed correlation between atherosclerosis and IA prevalence, future research should aim to elucidate the underlying pathophysiological mechanisms governing this relationship. To ensure the robustness and external validity of the findings, a prospective study design is essential, incorporating a sufficiently large and representative cohort to allow for the generalizability of results to the broader population. Such investigations could yield critical insights into the shared etiological pathways of systemic and cerebrovascular diseases, thereby enhancing risk stratification and informing the development of more precise preventive and therapeutic strategies.

The implications of initiating antithrombotic therapy in asymptomatic PAD patients based on abnormal ABI findings remain an area of ongoing investigation. While current evidence does not support the widespread prescription of antiplatelet therapy in this population, it is plausible that a subset of asymptomatic PAD patients, particularly those with markedly reduced ABI or additional CV risk factors, could benefit from targeted intervention. Future research is needed to establish precise

thresholds for intervention and to identify patient subgroups most likely to benefit from early therapeutic strategies.

Moreover, given the emerging evidence linking systemic vascular pathology to IAs, the routine assessment of ABI values in IA patients warrants investigation. Screening for PAD in this population could provide insights into the broader CV burden among IA patients and help refine primary prevention strategies for CV diseases. A prospective study assessing ABI in individuals diagnosed with IA could determine whether a low ABI value serves as a marker for heightened CV risk in this cohort. Such findings could support the integration of ABI screening into standard IA patient management, ultimately aiding in the early identification of individuals who may benefit from intensified CV risk reduction measures.

In conclusion, ABI measurement holds significant potential as a routine screening tool for CV risk stratification. Although the role of antithrombotic therapy in asymptomatic PAD remains uncertain, ongoing studies may clarify whether such interventions are warranted in patients with a low ABI. Additionally, expanding ABI screening to IA patients could provide valuable insights into the interplay between cerebrovascular and systemic vascular diseases, potentially informing more comprehensive preventive and therapeutic strategies.

7 Conclusions

The findings of the presented studies on the associations between peripheral pressure measurements and clinical outcomes can be summarized as follows:

1. Borderline ABI is associated with increased CV and all-cause mortality, suggesting that current ABI cut-offs may underestimate CV risk. A lower ABI threshold of 1.0 should be considered to improve risk assessment.
2. Incompressible ankle arteries are associated with increased mortality, and among these patients, lower TPs are linked to a worse prognosis.
3. The results suggest that low ABI and TBI values may be associated with an increased prevalence of IAs.

Acknowledgements

This dissertation project began in 2020. From that moment, this journey has taken me along a transformative path that has been both educational and inspiring. Along the way, I have been fortunate to receive the guidance, support, and encouragement of many individuals, to whom I am deeply grateful.

I wish to extend my deepest gratitude to my supervisors Harri Hakovirta, Petra Korpisalo and Dan Laukka, for their invaluable guidance and support throughout this project. I am particularly grateful to Harri for his tireless commitment and determined guidance, which were essential to the completion of this dissertation. Despite working in Saudi Arabia, he was consistently accessible and provided crucial guidance at pivotal moments. His words, "It's not enough to want to write it; it simply has to be done," have served as a constant source of motivation.

Special thanks go to Mirjami Laivuori for her significant contribution to the research. I also wish to express my appreciation to the reviewers, Velipekka Suominen and Jukka Huttunen, whose excellent observations helped clarify the key points of this dissertation and enhanced its scientific quality.

I want to thank my colleagues at the vascular surgery unit. I am especially grateful to Jan-Erik Wickström for being both a supportive shoulder and an inspiring discussion partner on my dissertation topic, and to Ville Rantasalo — without our shared office, the statistical analysis for the fourth study would never have been completed. Thanks to Päivi Helmiö, who made it possible to combine science and clinical work. Thank you, Veikko Nikulainen — you are the big brother I never had. I am also grateful to Emma Viikinkoski — it is always easy and pleasant to work with you. My thanks extend as well to Jussi Kärkkäinen, Jaakko Viljamaa, and Oskari Niiranen for the collaboration, insightful discussions, and humor they have brought, and to Kimmo Korhonen for being a safe and comforting “teddy bear father” throughout our shared professional journey.

I warmly remember my years working in Pori. I would like to thank Jorma Hannukainen for first introducing me to vascular surgery and inspiring my interest in the field, as well as Tuomas Koskinen for laying the foundation for my vascular surgery skills. Without you, I would not be on this path.

I am truly grateful to my friends, with whom I can always be my true self. Even during the busiest times, I have never had to fear that our friendship would fade. A special thanks goes to my friend Sini Keskinen for her help with the section on genetics.

I am deeply grateful to my parents, who have an unparalleled faith in me. Thank you, my mom Paula and dad Seppo, for always supporting me. I am also fortunate to have two amazing older sisters, Tiina and Tanja, whose determination and ambition have served as role models for me. Without you, I would not be who I am today.

To my dear husband, Samu — thank you for the beautiful illustration you created for my dissertation. I am grateful for your support throughout this project, as well as for your patience during the days when I was hidden away in my writing. Thank you for providing a therapeutic counterbalance through our home renovation project, and for bringing Alina and Olavi into my life to make it brighter. Most of all, thank you for sharing this life with me.

Finally, to my beloved Alvin and Leia — you have taught me more about life than anything else. You make me live in the moment and capture my full attention so completely that everything else fades away. You are the most meaningful part of my life, and I can't think of anything more valuable than the two of you. I am endlessly grateful and proud to have you both.

August 2025
Essi Kangas

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol*. 2020;76:2982-3021. doi: 10.1016/j.jacc.2020.11.010
2. Song P, Rudan D, Zhu Y, Fowkes FJI, Rahimi K, Fowkes FGR, Rudan I. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *Lancet Glob Health*. 2019;7:e1020-e1030. doi: 10.1016/s2214-109x(19)30255-4
3. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D. 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
4. AbuRahma AF, Adams E, AbuRahma J, Mata LA, Dean LS, Caron C, Sloan J. Critical analysis and limitations of resting ankle-brachial index in the diagnosis of symptomatic peripheral arterial disease patients and the role of diabetes mellitus and chronic kidney disease. *J Vasc Surg*. 2020;71:937-945. doi: 10.1016/j.jvs.2019.05.050
5. Gornik HL, Aronow HD, Goodney PP, Arya S, Brewster LP, Byrd L, Chandra V, Drachman DE, Eaves JM, Ehrman JK, et al. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS Guideline for the Management of Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149:e1313-e1410. doi: 10.1161/cir.0000000000001251
6. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *Jama*. 2008;300:197-208. doi: 10.1001/jama.300.2.197
7. Wickström JE, Virtanen J, Aro E, Jalkanen J, Venermo M, Hakovirta H. Bilateral low systolic toe pressure and toe-brachial index are associated with long-term mortality in patients with peripheral artery disease. *J Vasc Surg*. 2019;70:1994-2004. doi: 10.1016/j.jvs.2019.03.073
8. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol*. 2011;10:626-636. doi: 10.1016/s1474-4422(11)70109-0
9. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. 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. doi: 10.1016/s0140-6736(13)61249-0
10. Hirsch AT, Hartman L, Town RJ, Virnig BA. National health care costs of peripheral arterial disease in the Medicare population. *Vasc Med*. 2008;13:209-215. doi: 10.1177/1358863x08089277
11. Scully RE, Arnaoutakis DJ, DeBord Smith A, Semel M, Nguyen LL. Estimated annual health care expenditures in individuals with peripheral arterial disease. *J Vasc Surg*. 2018;67:558-567. doi: 10.1016/j.jvs.2017.06.102

12. Gersh BJ, Sliwa K, Mayosi BM, Yusuf S. Novel therapeutic concepts: the epidemic of cardiovascular disease in the developing world: global implications. *Eur Heart J*. 2010;31:642-648. doi: 10.1093/eurheartj/ehq030
13. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res*. 2015;116:1509-1526. doi: 10.1161/circresaha.116.303849
14. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *Jama*. 2001;286:1317-1324. doi: 10.1001/jama.286.11.1317
15. McDermott MM, Kerwin DR, Liu K, Martin GJ, O'Brien E, Kaplan H, Greenland P. Prevalence and significance of unrecognized lower extremity peripheral arterial disease in general medicine practice*. *J Gen Intern Med*. 2001;16:384-390. doi: 10.1046/j.1525-1497.2001.016006384.x
16. Grøndal N, Søgaard R, Lindholt JS. Baseline prevalence of abdominal aortic aneurysm, peripheral arterial disease and hypertension in men aged 65-74 years from a population screening study (VIVA trial). *Br J Surg*. 2015;102:902-906. doi: 10.1002/bjs.9825
17. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, Zakharyan A, Hirsch AT. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. *J Vasc Surg*. 2014;60:686-695.e682. doi: 10.1016/j.jvs.2014.03.290
18. Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Andersson B, Persson E, Wahlberg E. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *J Vasc Surg*. 2007;45:1185-1191. doi: 10.1016/j.jvs.2007.02.004
19. Sigvant B, Lundin F, 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. doi: 10.1016/j.ejvs.2015.10.022
20. Kumakura H, Kanai H, Hojo Y, Iwasaki T, Ichikawa S. Long-term survival and fate of the leg in de novo intermittent claudication. *Eur Heart J Qual Care Clin Outcomes*. 2017;3:208-215. doi: 10.1093/ehjqcco/qcw057
21. Sartipy F, Sigvant B, Lundin F, Wahlberg E. Ten Year Mortality in Different Peripheral Arterial Disease Stages: A Population Based Observational Study on Outcome. *Eur J Vasc Endovasc Surg*. 2018;55:529-536. doi: 10.1016/j.ejvs.2018.01.019
22. Hooi JD, Stoffers HE, Knottnerus JA, van Ree JW. The prognosis of non-critical limb ischaemia: a systematic review of population-based evidence. *Br J Gen Pract*. 1999;49:49-55.
23. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. 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
24. Roijers JP, Rakké YS, Hopmans CJ, Buimer MG, Ho GH, de Groot HGW, Veen EJ, Mulder PGH, van der Laan L. A mortality prediction model for elderly patients with critical limb ischemia. *J Vasc Surg*. 2020;71:2065-2072.e2062. doi: 10.1016/j.jvs.2019.08.245
25. Baubeta Fridh E, Andersson M, Thuresson M, Sigvant B, Kragsterman B, Johansson S, Hasvold P, Falkenberg M, Nordanstig J. Amputation Rates, Mortality, and Pre-operative Comorbidities in Patients Revascularised for Intermittent Claudication or Critical Limb Ischaemia: A Population Based Study. *Eur J Vasc Endovasc Surg*. 2017;54:480-486. doi: 10.1016/j.ejvs.2017.07.005
26. Kreutzburg T, Peters F, Kuchenbecker J, Marschall U, Lee R, Kriston L, Debus ES, Behrendt CA. Editor's Choice - The GermanVasc Score: A Pragmatic Risk Score Predicts Five Year Amputation Free Survival in Patients with Peripheral Arterial Occlusive Disease. *Eur J Vasc Endovasc Surg*. 2021;61:248-256. doi: 10.1016/j.ejvs.2020.11.013
27. Dormandy J, Belcher G, Broos P, Eikelboom B, Laszlo G, Konrad P, Moggi L, Mueller U. Prospective study of 713 below-knee amputations for ischaemia and the effect of a prostacyclin

analogue on healing. Hawaii Study Group. *Br J Surg*. 1994;81:33-37. doi: 10.1002/bjs.1800810110
28. Nigro P, Abe J, Berk BC. Flow shear stress and atherosclerosis: a matter of site specificity. *Antioxid Redox Signal*. 2011;15:1405-1414. doi: 10.1089/ars.2010.3679
29. VanderLaan PA, Reardon CA, Getz GS. Site specificity of atherosclerosis: site-selective responses to atherosclerotic modulators. *Arterioscler Thromb Vasc Biol*. 2004;24:12-22. doi: 10.1161/01.ATV.0000105054.43931.f0
30. Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. *Circulation*. 2004;109:Iii27-32. doi: 10.1161/01.CIR.0000131515.03336.f8
31. Gimbrone MA, Jr., García-Cardeña G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. *Circ Res*. 2016;118:620-636. doi: 10.1161/circresaha.115.306301
32. Skålén K, Gustafsson M, Rydberg EK, Hultén LM, Wiklund O, Innerarity TL, Borén J. Subendothelial retention of atherogenic lipoproteins in early atherosclerosis. *Nature*. 2002;417:750-754. doi: 10.1038/nature00804
33. Galkina E, Ley K. Vascular adhesion molecules in atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2007;27:2292-2301. doi: 10.1161/atvbaha.107.149179
34. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. *Nature*. 2011;473:317-325. doi: 10.1038/nature10146
35. Gisterå A, Hansson GK. The immunology of atherosclerosis. *Nat Rev Nephrol*. 2017;13:368-380. doi: 10.1038/nrneph.2017.51
36. Bentzon JF, Weile C, Sondergaard CS, Hindkjaer J, Kassem M, Falk E. Smooth muscle cells in atherosclerosis originate from the local vessel wall and not circulating progenitor cells in ApoE knockout mice. *Arterioscler Thromb Vasc Biol*. 2006;26:2696-2702. doi: 10.1161/01.ATV.0000247243.48542.9d
37. Feil S, Hofmann F, Feil R. SM22alpha modulates vascular smooth muscle cell phenotype during atherogenesis. *Circ Res*. 2004;94:863-865. doi: 10.1161/01.Res.0000126417.38728.F6
38. Hansson GK, Hermansson A. The immune system in atherosclerosis. *Nat Immunol*. 2011;12:204-212. doi: 10.1038/ni.2001
39. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res*. 2014;114:1852-1866. doi: 10.1161/circresaha.114.302721
40. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature*. 1993;362:801-809. doi: 10.1038/362801a0
41. Lanzer P, Ferraresi R. Medial Sclerosis-Epidemiology and Clinical Significance. *Dtsch Arztebl Int*. 2023;120:365-372. doi: 10.3238/arztebl.m2023.0066
42. Lanzer P, Boehm M, Sorribas V, Thiriet M, Janzen J, Zeller T, St Hilaire C, Shanahan C. Medial vascular calcification revisited: review and perspectives. *Eur Heart J*. 2014;35:1515-1525. doi: 10.1093/eurheartj/ehu163
43. Alappan HR, Kaur G, Manzoor S, Navarrete J, O'Neill WC. Warfarin Accelerates Medial Arterial Calcification in Humans. *Arterioscler Thromb Vasc Biol*. 2020;40:1413-1419. doi: 10.1161/atvbaha.119.313879
44. Kapustin AN, Shanahan CM. Calcium regulation of vascular smooth muscle cell-derived matrix vesicles. *Trends Cardiovasc Med*. 2012;22:133-137. doi: 10.1016/j.tcm.2012.07.009
45. Yang W, Zou B, Hou Y, Yan W, Chen T, Qu S. Extracellular vesicles in vascular calcification. *Clin Chim Acta*. 2019;499:118-122. doi: 10.1016/j.cca.2019.09.002
46. O'Neill WC, Han KH, Schneider TM, Hennigar RA. Prevalence of nonatheromatous lesions in peripheral arterial disease. *Arterioscler Thromb Vasc Biol*. 2015;35:439-447. doi: 10.1161/atvbaha.114.304764
47. Lanzer P, Hannan FM, Lanzer JD, Janzen J, Raggi P, Furniss D, Schuchardt M, Thakker R, Fok PW, Saez-Rodriguez J, et al. Medial Arterial Calcification: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2021;78:1145-1165. doi: 10.1016/j.jacc.2021.06.049

48. Nikolajević J, Šabovič M. Inflammatory, Metabolic, and Coagulation Effects on Medial Arterial Calcification in Patients with Peripheral Arterial Disease. *Int J Mol Sci*. 2023;24. doi: 10.3390/ijms24043132
49. Weber T, Chirinos JA. Pulsatile arterial haemodynamics in heart failure. *Eur Heart J*. 2018;39:3847-3854. doi: 10.1093/eurheartj/ehy346
50. Mitchell GF. Aortic stiffness, pressure and flow pulsatility, and target organ damage. *J Appl Physiol (1985)*. 2018;125:1871-1880. doi: 10.1152/japplphysiol.00108.2018
51. Tarvainen S, Wirth G, Juusola G, Hautero O, Kalliokoski K, Sjöros T, Nikulainen V, Taavitsainen J, Hytönen J, Frimodig C, et al. Critical limb-threatening ischaemia and microvascular transformation: clinical implications. *Eur Heart J*. 2024;45:255-264. doi: 10.1093/eurheartj/ehad562
52. Zwakenberg SR, de Jong PA, Hendriks EJ, Westerink J, Spiering W, de Borst GJ, Cramer MJ, Bartstra JW, Doesburg T, Rutters F, et al. Intimal and medial calcification in relation to cardiovascular risk factors. *PLoS One*. 2020;15:e0235228. doi: 10.1371/journal.pone.0235228
53. Fok PW, Lanzer P. Media sclerosis drives and localizes atherosclerosis in peripheral arteries. *PLoS One*. 2018;13:e0205599. doi: 10.1371/journal.pone.0205599
54. Losurdo F, Ferraresi R, Ucci A, Zanetti A, Clerici G, Zambon A. Association of infrapopliteal medial arterial calcification with lower-limb amputations in high-risk patients: A systematic review and meta-analysis. *Vasc Med*. 2021;26:164-173. doi: 10.1177/1358863x20979738
55. Kim TI, Guzman RJ. Medial artery calcification in peripheral artery disease. *Front Cardiovasc Med*. 2023;10:1093355. doi: 10.3389/fcvm.2023.1093355
56. Vos A, de Jong PA, Verdoorn D, Mali W, Bleys R, Vink A. Histopathological characterization of intimal lesions and arterial wall calcification in the arteries of the leg of elderly cadavers. *Clin Anat*. 2021;34:835-841. doi: 10.1002/ca.23701
57. Narula N, Dannenberg AJ, Olin JW, Bhatt DL, Johnson KW, Nadkarni G, Min J, Torii S, Poojary P, Anand SS, et al. Pathology of Peripheral Artery Disease in Patients With Critical Limb Ischemia. *J Am Coll Cardiol*. 2018;72:2152-2163. doi: 10.1016/j.jacc.2018.08.002
58. Diehm N, Shang A, Silvestro A, Do DD, Dick F, Schmidli J, Mahler F, Baumgartner I. Association of Cardiovascular Risk Factors with Pattern of Lower Limb Atherosclerosis in 2659 Patients Undergoing Angioplasty. *European Journal of Vascular and Endovascular Surgery*. 2006;31:59-63. doi: 10.1016/j.ejvs.2005.09.006
59. Levin MG, Klarin D, Assimes TL, Freiberg MS, Ingelsson E, Lynch J, Natarajan P, O'Donnell C, Rader DJ, Tsao PS, et al. Genetics of Smoking and Risk of Atherosclerotic Cardiovascular Diseases: A Mendelian Randomization Study. *JAMA Netw Open*. 2021;4:e2034461. doi: 10.1001/jamanetworkopen.2020.34461
60. Ding N, Sang Y, Chen J, Ballew SH, Kalbaugh CA, Salameh MJ, Blaha MJ, Allison M, Heiss G, Selvin E, et al. Cigarette Smoking, Smoking Cessation, and Long-Term Risk of 3 Major Atherosclerotic Diseases. *J Am Coll Cardiol*. 2019;74:498-507. doi: 10.1016/j.jacc.2019.05.049
61. Fowkes FG, Housley E, Riemersma RA, Macintyre CC, Cawood EH, Prescott RJ, Ruckley CV. Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. *Am J Epidemiol*. 1992;135:331-340. doi: 10.1093/oxfordjournals.aje.a116294
62. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *Jama*. 2002;287:2570-2581. doi: 10.1001/jama.287.19.2570
63. Dick F, Diehm N, Galimanis A, Husmann M, Schmidli J, Baumgartner I. Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. *J Vasc Surg*. 2007;45:751-761. doi: 10.1016/j.jvs.2006.12.022
64. Marso SP, Hiatt WR. Peripheral arterial disease in patients with diabetes. *J Am Coll Cardiol*. 2006;47:921-929. doi: 10.1016/j.jacc.2005.09.065

65. Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D, Uccioli L, Urbancic V, Bakker K, Holstein P, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. *Diabetologia*. 2008;51:747-755. doi: 10.1007/s00125-008-0940-0
66. Goodney PP, Tarulli M, Faerber AE, Schanzer A, Zwolak RM. Fifteen-year trends in lower limb amputation, revascularization, and preventive measures among medicare patients. *JAMA Surg*. 2015;150:84-86. doi: 10.1001/jamasurg.2014.1007
67. Geiss LS, Li Y, Hora I, Albright A, Rolka D, Gregg EW. Resurgence of Diabetes-Related Nontraumatic Lower-Extremity Amputation in the Young and Middle-Aged Adult U.S. Population. *Diabetes Care*. 2019;42:50-54. doi: 10.2337/dc18-1380
68. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes Care*. 2001;24:1433-1437. doi: 10.2337/diacare.24.8.1433
69. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med*. 2004;141:421-431. doi: 10.7326/0003-4819-141-6-200409210-00007
70. Lehto S, Niskanen L, Suhonen M, Rönnemaa T, Laakso M. Medial artery calcification. A neglected harbinger of cardiovascular complications in non-insulin-dependent diabetes mellitus. *Arterioscler Thromb Vasc Biol*. 1996;16:978-983. doi: 10.1161/01.atv.16.8.978
71. Moon JS, Clark VM, Beabout JW, Swee RG, Dyck PJ. A controlled study of medial arterial calcification of legs: implications for diabetic polyneuropathy. *Arch Neurol*. 2011;68:1290-1294. doi: 10.1001/archneurol.2011.211
72. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:1269-1324. doi: 10.1161/hyp.0000000000000066
73. Hooi JD, Kester AD, Stoffers HE, Overdijk MM, van Ree JW, Knottnerus JA. Incidence of and risk factors for asymptomatic peripheral arterial occlusive disease: a longitudinal study. *Am J Epidemiol*. 2001;153:666-672. doi: 10.1093/aje/153.7.666
74. Meijer WT, Grobbee DE, Hunink MG, Hofman A, Hoes AW. Determinants of peripheral arterial disease in the elderly: the Rotterdam study. *Arch Intern Med*. 2000;160:2934-2938. doi: 10.1001/archinte.160.19.2934
75. Safar ME, Priollet P, Luizy F, Mourad JJ, Cacoub P, Levesque H, Benelbaz J, Michon P, Herrmann MA, Blacher J. Peripheral arterial disease and isolated systolic hypertension: the ATTEST study. *J Hum Hypertens*. 2009;23:182-187. doi: 10.1038/jhh.2008.121
76. Makin A, Lip GY, Silverman S, Beevers DG. Peripheral vascular disease and hypertension: a forgotten association? *J Hum Hypertens*. 2001;15:447-454. doi: 10.1038/sj.jhh.1001209
77. Kou M, Ding N, Ballew SH, Salameh MJ, Martin SS, Selvin E, Heiss G, Ballantyne CM, Matsushita K, Hoogeveen RC. Conventional and Novel Lipid Measures and Risk of Peripheral Artery Disease. *Arterioscler Thromb Vasc Biol*. 2021;41:1229-1238. doi: 10.1161/atvbaha.120.315828
78. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *Jama*. 2001;285:2481-2485. doi: 10.1001/jama.285.19.2481
79. Aday AW, Lawler PR, Cook NR, Ridker PM, Mora S, Pradhan AD. Lipoprotein Particle Profiles, Standard Lipids, and Peripheral Artery Disease Incidence. *Circulation*. 2018;138:2330-2341. doi: 10.1161/circulationaha.118.035432

80. Kennedy M, Solomon C, Manolio TA, Criqui MH, Newman AB, Polak JF, Burke GL, Enright P, Cushman M. Risk factors for declining ankle-brachial index in men and women 65 years or older: the Cardiovascular Health Study. *Arch Intern Med*. 2005;165:1896-1902. doi: 10.1001/archinte.165.16.1896
81. 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. doi: 10.1016/j.jvs.2006.12.054
82. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, Kuder J, Murphy SA, Jukema JW, Lewis BS, et al. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation*. 2018;137:338-350. doi: 10.1161/circulationaha.117.032235
83. Samavarchitehrani A, Cannavo A, Behnoush AH, Kazemi Abadi A, Shokri Varniab Z, Khalaji A. Investigating the association between the triglyceride-glucose index and peripheral artery disease: a systematic review and meta-analysis. *Nutr Diabetes*. 2024;14:80. doi: 10.1038/s41387-024-00341-y
84. Matsushita K, Ballew SH, Coresh J, Arima H, Ärnlöv J, Cirillo M, Ebert N, Hiramoto JS, Kimm H, Shlipak MG, et al. Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol*. 2017;5:718-728. doi: 10.1016/s2213-8587(17)30183-3
85. Wattanakit K, Folsom AR, Selvin E, Coresh J, Hirsch AT, Weatherley BD. Kidney function and risk of peripheral arterial disease: results from the Atherosclerosis Risk in Communities (ARIC) Study. *J Am Soc Nephrol*. 2007;18:629-636. doi: 10.1681/asn.2005111204
86. Selvin E, Köttgen A, Coresh J. Kidney function estimated from serum creatinine and cystatin C and peripheral arterial disease in NHANES 1999-2002. *Eur Heart J*. 2009;30:1918-1925. doi: 10.1093/eurheartj/ehp195
87. Leskinen Y, Salenius JP, Lehtimäki T, Huhtala H, Saha H. The prevalence of peripheral arterial disease and medial arterial calcification in patients with chronic renal failure: requirements for diagnostics. *Am J Kidney Dis*. 2002;40:472-479. doi: 10.1053/ajkd.2002.34885
88. Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, Strippoli GF. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *Jama*. 2011;305:1119-1127. doi: 10.1001/jama.2011.308
89. Kono K, Fujii H, Nakai K, Goto S, Shite J, Hirata K, Fukagawa M, Nishi S. Composition and plaque patterns of coronary culprit lesions and clinical characteristics of patients with chronic kidney disease. *Kidney Int*. 2012;82:344-351. doi: 10.1038/ki.2012.118
90. London GM, Guérin AP, Marchais SJ, Métivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant*. 2003;18:1731-1740. doi: 10.1093/ndt/gfg414
91. Schwarz U, Buzello M, Ritz E, Stein G, Raabe G, Wiest G, Mall G, Amann K. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. *Nephrol Dial Transplant*. 2000;15:218-223. doi: 10.1093/ndt/15.2.218
92. Eraso LH, Fukaya E, Mohler ER, 3rd, Xie D, Sha D, Berger JS. Peripheral arterial disease, prevalence and cumulative risk factor profile analysis. *Eur J Prev Cardiol*. 2014;21:704-711. doi: 10.1177/2047487312452968
93. Joosten MM, Pai JK, Bertoia ML, Rimm EB, Spiegelman D, Mittleman MA, Mukamal KJ. Associations between conventional cardiovascular risk factors and risk of peripheral artery disease in men. *Jama*. 2012;308:1660-1667. doi: 10.1001/jama.2012.13415

94. Wang JC, Bennett M. Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence. *Circ Res*. 2012;111:245-259. doi: 10.1161/circresaha.111.261388
95. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr., et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735-2752. doi: 10.1161/circulationaha.105.169404
96. Tune JD, Goodwill AG, Sassoon DJ, Mather KJ. Cardiovascular consequences of metabolic syndrome. *Transl Res*. 2017;183:57-70. doi: 10.1016/j.trsl.2017.01.001
97. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, Montori VM. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49:403-414. doi: 10.1016/j.jacc.2006.09.032
98. Li X, Li X, Lin H, Fu X, Lin W, Li M, Zeng X, Gao Q. Metabolic syndrome and stroke: A meta-analysis of prospective cohort studies. *J Clin Neurosci*. 2017;40:34-38. doi: 10.1016/j.jocn.2017.01.018
99. Garg PK, Biggs ML, Carnethon M, Ix JH, Criqui MH, Britton KA, Djoussé L, Sutton-Tyrrell K, Newman AB, Cushman M, Mukamal KJ. Metabolic syndrome and risk of incident peripheral artery disease: the cardiovascular health study. *Hypertension*. 2014;63:413-419. doi: 10.1161/hypertensionaha.113.01925
100. Gao L, Zhao W, Liu Q, Qin M. Association Between Metabolic Syndrome and Peripheral Arterial Disease in Elderly Patients with Type 2 Diabetes. *Diabetes Metab Syndr Obes*. 2021;14:4783-4789. doi: 10.2147/dmso.S343441
101. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med*. 2017;377:13-27. doi: 10.1056/NEJMoa1614362
102. Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, Sarwar N, Kizer JR, Lawlor DA, Nordestgaard BG, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet*. 2011;377:1085-1095. doi: 10.1016/s0140-6736(11)60105-0
103. Hajibandeh S, Hajibandeh S, Shah S, Child E, Antoniou GA, Torella F. Prognostic significance of ankle brachial pressure index: A systematic review and meta-analysis. *Vascular*. 2017;25:208-224. doi: 10.1177/1708538116658392
104. Berg J, Björck L, Lappas G, O'Flaherty M, Capewell S, Rosengren A. Continuing decrease in coronary heart disease mortality in Sweden. *BMC Cardiovasc Disord*. 2014;14:9. doi: 10.1186/1471-2261-14-9
105. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, Kissela BM, Kittner SJ, Lichtman JH, Lisabeth LD, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:315-353. doi: 10.1161/01.str.0000437068.30550.cf
106. Sigvant B, Hasvold P, Kragsterman B, Falkenberg M, Johansson S, Thuresson M, Nordanstig J. Cardiovascular outcomes in patients with peripheral arterial disease as an initial or subsequent manifestation of atherosclerotic disease: Results from a Swedish nationwide study. *J Vasc Surg*. 2017;66:507-514.e501. doi: 10.1016/j.jvs.2017.01.067
107. Kochar A, Mulder H, Rockhold FW, Baumgartner I, Berger JS, Blomster JI, Fowkes FGR, Katona BG, Lopes RD, Al-Khalidi HR, et al. Cause of Death Among Patients With Peripheral Artery Disease: Insights From the EUCLID Trial. *Circ Cardiovasc Qual Outcomes*. 2020;13:e006550. doi: 10.1161/circoutcomes.120.006550
108. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, Goto S, Liau CS, Richard AJ, Röther J, Wilson PW. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *Jama*. 2006;295:180-189. doi: 10.1001/jama.295.2.180

109. Gutierrez JA, Aday AW, Patel MR, Jones WS. Polyvascular Disease: Reappraisal of the Current Clinical Landscape. *Circ Cardiovasc Interv*. 2019;12:e007385. doi: 10.1161/circinterventions.119.007385
110. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, Wilson PW, Alberts MJ, D'Agostino R, Liau CS, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *Jama*. 2010;304:1350-1357. doi: 10.1001/jama.2010.1322
111. Hirsh J, Bhatt DL. Comparative benefits of clopidogrel and aspirin in high-risk patient populations: lessons from the CAPRIE and CURE studies. *Arch Intern Med*. 2004;164:2106-2110. doi: 10.1001/archinte.164.19.2106
112. Gutierrez JA, Mulder H, Jones WS, Rockhold FW, Baumgartner I, Berger JS, Blomster JI, Fowkes FGR, Held P, Katona BG, et al. Polyvascular Disease and Risk of Major Adverse Cardiovascular Events in Peripheral Artery Disease: A Secondary Analysis of the EUCLID Trial. *JAMA Netw Open*. 2018;1:e185239. doi: 10.1001/jamanetworkopen.2018.5239
113. Bonaca MP, Gutierrez JA, Cannon C, Giugliano R, Blazing M, Park JG, White J, Tershakovec A, Braunwald E. Polyvascular disease, type 2 diabetes, and long-term vascular risk: a secondary analysis of the IMPROVE-IT trial. *Lancet Diabetes Endocrinol*. 2018;6:934-943. doi: 10.1016/s2213-8587(18)30290-0
114. Suárez C, Zeymer U, Limbourg T, Baumgartner I, Cacoub P, Poldermans D, Röther J, Bhatt DL, Steg PG. Influence of polyvascular disease on cardiovascular event rates. Insights from the REACH Registry. *Vasc Med*. 2010;15:259-265. doi: 10.1177/1358863x10373299
115. Colantonio LD, Hubbard D, Monda KL, Mues KE, Huang L, Dai Y, Jackson EA, Brown TM, Rosenson RS, Woodward M, et al. Atherosclerotic Risk and Statin Use Among Patients With Peripheral Artery Disease. *J Am Coll Cardiol*. 2020;76:251-264. doi: 10.1016/j.jacc.2020.05.048
116. Sadeghi M, Heidari R, Mostanfar B, Tavassoli A, Roghani F, Yazdekhasti S. The Relation Between Ankle-Brachial Index (ABI) and Coronary Artery Disease Severity and Risk Factors: An Angiographic Study. *ARYA Atheroscler*. 2011;7:68-73.
117. Caro J, Migliaccio-Walle K, Ishak KJ, Proskorovsky I. 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
118. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med*. 2017;376:1713-1722. doi: 10.1056/NEJMoa1615664
119. Tsai S, Vega GL. Coronary and peripheral artery plaques: do differences in plaque characteristics translate to differences in lipid management? *J Investig Med*. 2020;68:1141-1151. doi: 10.1136/jim-2019-001252
120. Almeida SO, Budoff M. Effect of statins on atherosclerotic plaque. *Trends Cardiovasc Med*. 2019;29:451-455. doi: 10.1016/j.tcm.2019.01.001
121. Davì G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med*. 2007;357:2482-2494. doi: 10.1056/NEJMra071014
122. Cyrus T, Sung S, Zhao L, Funk CD, Tang S, Praticò D. Effect of low-dose aspirin on vascular inflammation, plaque stability, and atherogenesis in low-density lipoprotein receptor-deficient mice. *Circulation*. 2002;106:1282-1287. doi: 10.1161/01.cir.0000027816.54430.96
123. Heitzer T, Rudolph V, Schwedhelm E, Karstens M, Sydow K, Ortak M, Tschentscher P, Meinertz T, Böger R, Baldus S. Clopidogrel improves systemic endothelial nitric oxide bioavailability in patients with coronary artery disease: evidence for antioxidant and antiinflammatory effects. *Arterioscler Thromb Vasc Biol*. 2006;26:1648-1652. doi: 10.1161/01.ATV.0000225288.74170.dc
124. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Bmj*. 2002;324:71-86. doi: 10.1136/bmj.324.7329.71

125. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet*. 1996;348:1329-1339. doi: 10.1016/s0140-6736(96)09457-3
126. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, et al. Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease. *N Engl J Med*. 2017;376:32-40. doi: 10.1056/NEJMoa1611688
127. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, Aboyans V, Alings M, Kakkar AK, Keltai K, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018;391:219-229. doi: 10.1016/s0140-6736(17)32409-1
128. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, Fanelli F, Capell WH, Diao L, Jaeger N, et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. *N Engl J Med*. 2020;382:1994-2004. doi: 10.1056/NEJMoa2000052
129. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373:1849-1860. doi: 10.1016/s0140-6736(09)60503-1
130. Safar ME, Protogerou AD, Blacher J. Statins, central blood pressure, and blood pressure amplification. *Circulation*. 2009;119:9-12. doi: 10.1161/circulationaha.108.824532
131. Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley Diabetes Study. *Circulation*. 1995;91:1472-1479. doi: 10.1161/01.cir.91.5.1472
132. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, Mills JL, Ricco JB, Suresh KR, Murad MH. Global vascular guidelines on the management of chronic limb-threatening ischemia. *J Vasc Surg*. 2019;69:3S-125S.e140. doi: 10.1016/j.jvs.2019.02.016
133. Dachun X, Jue L, Liling Z, Yawei X, Dayi H, Pagoto SL, Yunsheng M. Sensitivity and specificity of the ankle--brachial index to diagnose peripheral artery disease: a structured review. *Vasc Med*. 2010;15:361-369. doi: 10.1177/1358863x10378376
134. Herraiz-Adillo Á, Cavero-Redondo I, Álvarez-Bueno C, Pozuelo-Carrascosa DP, Solera-Martínez M. The accuracy of toe brachial index and ankle brachial index in the diagnosis of lower limb peripheral arterial disease: A systematic review and meta-analysis. *Atherosclerosis*. 2020;315:81-92. doi: 10.1016/j.atherosclerosis.2020.09.026
135. Williams DT, Harding KG, Price P. An evaluation of the efficacy of methods used in screening for lower-limb arterial disease in diabetes. *Diabetes Care*. 2005;28:2206-2210. doi: 10.2337/diacare.28.9.2206
136. Heald CL, Fowkes FG, Murray GD, Price JF. 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
137. Alahdab F, Wang AT, Elraiyah TA, Malgor RD, Rizvi AZ, Lane MA, Prokop LJ, Montori VM, Conte MS, Murad MH. 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
138. Criqui MH, Ninomiya JK, Wingard DL, Ji M, Fronek A. Progression of peripheral arterial disease predicts cardiovascular disease morbidity and mortality. *J Am Coll Cardiol*. 2008;52:1736-1742. doi: 10.1016/j.jacc.2008.07.060
139. Feringa HH, Karagiannis SE, Schouten O, Vidakovic R, van Waning VH, Boersma E, Welten G, Bax JJ, Poldermans D. Prognostic significance of declining ankle-brachial index values in patients with suspected or known peripheral arterial disease. *Eur J Vasc Endovasc Surg*. 2007;34:206-213. doi: 10.1016/j.ejvs.2007.02.018
140. Diehm C, Lange S, Darius H, Pittrow D, von Stritzky B, Tepohl G, Haberl RL, Allenberg JR, Dasch B, Trampisch HJ. Association of low ankle brachial index with high mortality in primary care. *Eur Heart J*. 2006;27:1743-1749. doi: 10.1093/eurheartj/ehl092

141. O'Hare AM, Katz R, Shlipak MG, Cushman M, Newman AB. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. *Circulation*. 2006;113:388-393. doi: 10.1161/circulationaha.105.570903
142. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, Fowkes FG, Hiatt WR, Jönsson B, Lacroix P, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation*. 2012;126:2890-2909. doi: 10.1161/CIR.0b013e318276fbcb
143. Tanaka S, Kaneko H, Kano H, Matsuno S, Suzuki S, Takai H, Otsuka T, Uejima T, Oikawa Y, Nagashima K, et al. The predictive value of the borderline ankle-brachial index for long-term clinical outcomes: An observational cohort study. *Atherosclerosis*. 2016;250:69-76. doi: 10.1016/j.atherosclerosis.2016.05.014
144. Alzamora MT, Forés R, Pera G, Baena-Díez JM, Valverde M, Torán P. Low, borderline and normal ankle-brachial index as a predictor of incidents outcomes in the Mediterranean based-population ARTPER cohort after 9 years follow-up. *PLoS One*. 2019;14:e0209163. doi: 10.1371/journal.pone.0209163
145. Paskiewicz A, Wang FM, Yang C, Ballew SH, Kalbaugh CA, Selvin E, Salameh M, Heiss G, Coresh J, Matsushita K. Ankle-Brachial Index and Subsequent Risk of Severe Ischemic Leg Outcomes: The ARIC Study. *J Am Heart Assoc*. 2021;10:e021801. doi: 10.1161/jaha.121.021801
146. McDermott MM, Guralnik JM, Tian L, Liu K, Ferrucci L, Liao Y, Sharma L, Criqui MH. Associations of borderline and low normal ankle-brachial index values with functional decline at 5-year follow-up: the WALCS (Walking and Leg Circulation Study). *J Am Coll Cardiol*. 2009;53:1056-1062. doi: 10.1016/j.jacc.2008.09.063
147. Suominen V, Rantanen T, Venermo M, Saarinen J, Salenius J. Prevalence and risk factors of PAD among patients with elevated ABI. *Eur J Vasc Endovasc Surg*. 2008;35:709-714. doi: 10.1016/j.ejvs.2008.01.013
148. Moussa Pacha H, Mallipeddi VP, Afzal N, Moon S, Kaggal VC, Kalra M, Oderich GS, Wennberg PW, Rooke TW, Scott CG, et al. Association of Ankle-Brachial Indices With Limb Revascularization or Amputation in Patients With Peripheral Artery Disease. *JAMA Netw Open*. 2018;1:e185547. doi: 10.1001/jamanetworkopen.2018.5547
149. Allison MA, Hiatt WR, Hirsch AT, Coll JR, Criqui MH. A high ankle-brachial index is associated with increased cardiovascular disease morbidity and lower quality of life. *J Am Coll Cardiol*. 2008;51:1292-1298. doi: 10.1016/j.jacc.2007.11.064
150. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, Howard BV. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. *Circulation*. 2004;109:733-739. doi: 10.1161/01.Cir.0000112642.63927.54
151. Gu X, Man C, Zhang H, Fan Y. High ankle-brachial index and risk of cardiovascular or all-cause mortality: A meta-analysis. *Atherosclerosis*. 2019;282:29-36. doi: 10.1016/j.atherosclerosis.2018.12.028
152. Chen HY, Wei F, Wang LH, Wang Z, Meng J, Yu HB, Zhang RN, Sun GJ, Jiang AL, Wang L. Abnormal ankle-brachial index and risk of cardiovascular or all-cause mortality in patients with chronic kidney disease: a meta-analysis. *J Nephrol*. 2017;30:493-501. doi: 10.1007/s40620-017-0376-z
153. Laivuori M, Hakovirta H, Kauhanen P, Sinisalo J, Sund R, Albäck A, Venermo M. Toe pressure should be part of a vascular surgeon's first-line investigation in the assessment of lower extremity artery disease and cardiovascular risk of a patient. *J Vasc Surg*. 2021;73:641-649.e643. doi: 10.1016/j.jvs.2020.06.104
154. Parmar GM, Tanikella R, Gupta K, Dicks AB, Sakhuja R, Schainfeld R, Dua A, Weinberg I. High ankle-brachial index participants experienced similar long-term mortality as peripheral artery disease in a national sample of community-dwelling adults. *J Vasc Surg*. 2024;80:1251-1259. doi: 10.1016/j.jvs.2024.06.005

155. Suominen V, Uurto I, Saarinen J, Venermo M, Salenius J. PAD as a risk factor for mortality among patients with elevated ABI--a clinical study. *Eur J Vasc Endovasc Surg*. 2010;39:316-322. doi: 10.1016/j.ejvs.2009.12.003
156. Criqui MH, McClelland RL, McDermott MM, Allison MA, Blumenthal RS, Aboyans V, Ix JH, Burke GL, Liu K, Shea S. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2010;56:1506-1512. doi: 10.1016/j.jacc.2010.04.060
157. Høyer C, Høgh AL, Sandermann J, Zacho HD, Petersen LJ. Risk factors and haemodynamic variables in patients with low toe-brachial index but normal ankle-brachial index. *Atherosclerosis*. 2019;289:21-26. doi: 10.1016/j.atherosclerosis.2019.08.005
158. Shishehbor MH, Hammad TA, Zeller T, Baumgartner I, Scheinert D, Rocha-Singh KJ. An analysis of IN.PACT DEEP randomized trial on the limitations of the societal guidelines-recommended hemodynamic parameters to diagnose critical limb ischemia. *J Vasc Surg*. 2016;63:1311-1317. doi: 10.1016/j.jvs.2015.11.042
159. Nordanstig J, Behrendt CA, Baumgartner I, Belch J, Bäck M, Fitridge R, Hinchliffe R, Lejay A, Mills JL, Rother U, et al. Editor's Choice -- European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Asymptomatic Lower Limb Peripheral Arterial Disease and Intermittent Claudication. *Eur J Vasc Endovasc Surg*. 2024;67:9-96. doi: 10.1016/j.ejvs.2023.08.067
160. Mills JL, Sr., Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, Andros G. 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. doi: 10.1016/j.jvs.2013.08.003
161. Hyun S, Forbang NI, Allison MA, Denenberg JO, Criqui MH, Ix JH. Ankle-brachial index, toe-brachial index, and cardiovascular mortality in persons with and without diabetes mellitus. *J Vasc Surg*. 2014;60:390-395. doi: 10.1016/j.jvs.2014.02.008
162. Wickström JE, Laivuori M, Aro E, Sund RT, Hautero O, Venermo M, Jalkanen J, Hakovirta H. Toe Pressure and Toe Brachial Index are Predictive of Cardiovascular Mortality, Overall Mortality, and Amputation Free Survival in Patients with Peripheral Artery Disease. *Eur J Vasc Endovasc Surg*. 2017;53:696-703. doi: 10.1016/j.ejvs.2017.02.012
163. Hishida M, Imaizumi T, Menez S, Okazaki M, Akiyama S, Kasuga H, Ishigami J, Maruyama S, Matsushita K. Additional prognostic value of toe-brachial index beyond ankle-brachial index in hemodialysis patients. *BMC Nephrol*. 2020;21:353. doi: 10.1186/s12882-020-01991-7
164. Sonter JA, Chuter VH. Cross-sectional correlations between the toe brachial index and lower limb complications in older people. *Int Wound J*. 2017;14:74-78. doi: 10.1111/iwj.12552
165. Salaun P, Desormais I, Lapébie FX, Rivière AB, Aboyans V, Lacroix P, Bataille V, Constans J, Boulon C. Comparison of Ankle Pressure, Systolic Toe Pressure, and Transcutaneous Oxygen Pressure to Predict Major Amputation After 1 Year in the COPART Cohort. *Angiology*. 2019;70:229-236. doi: 10.1177/0003319718793566
166. Dinger TF, Darkwah Oppong M, Park C, Said M, Chihi M, Rauschenbach L, Gembruch O, Deuschl C, Wrede KH, Lenz V, et al. Development of multiple intracranial aneurysms: beyond the common risk factors. *Journal of Neurosurgery*. 2022;137:1056-1063. doi: https://doi.org/10.3171/2021.11.JNS212325
167. Jabbarli R, Dinger TF, Darkwah Oppong M, Pierscianek D, Dammann P, Wrede KH, Kaier K, Köhrmann M, Forsting M, Kleinschnitz C, Sure U. Risk Factors for and Clinical Consequences of Multiple Intracranial Aneurysms: A Systematic Review and Meta-Analysis. *Stroke*. 2018;49:848-855. doi: 10.1161/strokeaha.117.020342
168. Korja M, Lehto H, Juvela S, Kaprio J. Incidence of subarachnoid hemorrhage is decreasing together with decreasing smoking rates. *Neurology*. 2016;87:1118-1123. doi: 10.1212/wnl.0000000000003091

169. Korja M, Silventoinen K, Laatikainen T, Jousilahti P, Salomaa V, Kaprio J. Cause-specific mortality of 1-year survivors of subarachnoid hemorrhage. *Neurology*. 2013;80:481-486. doi: 10.1212/WNL.0b013e31827f0fb5
170. Ingall T, Asplund K, Mähönen M, Bonita R. A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. *Stroke*. 2000;31:1054-1061. doi: 10.1161/01.str.31.5.1054
171. Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. *Lancet Neurol*. 2009;8:635-642. doi: 10.1016/s1474-4422(09)70126-7
172. Rinkel GJ, Algra A. Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. *Lancet Neurol*. 2011;10:349-356. doi: 10.1016/s1474-4422(11)70017-5
173. Passier PE, Visser-Meily JM, van Zandvoort MJ, Post MW, Rinkel GJ, van Heugten C. Prevalence and determinants of cognitive complaints after aneurysmal subarachnoid hemorrhage. *Cerebrovasc Dis*. 2010;29:557-563. doi: 10.1159/000306642
174. Thompson BG, Brown RD, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES, Duckwiler GR, Harris CC, Howard VJ, Johnston SC, et al. Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms. *Stroke*. 2015;46:2368-2400. doi: 10.1161/str.0000000000000070
175. Etminan N, Chang HS, Hackenberg K, de Rooij NK, Vergouwen MDI, Rinkel GJE, Algra A. Worldwide Incidence of Aneurysmal Subarachnoid Hemorrhage According to Region, Time Period, Blood Pressure, and Smoking Prevalence in the Population: A Systematic Review and Meta-analysis. *JAMA Neurol*. 2019;76:588-597. doi: 10.1001/jamaneurol.2019.0006
176. Xia C, Hoffman H, Anikpezie N, Philip K, Wee C, Choudhry R, Albright KC, Masoud H, Beutler T, Schmidt E, et al. Trends in the Incidence of Spontaneous Subarachnoid Hemorrhages in the United States, 2007-2017. *Neurology*. 2023;100:e123-e132. doi: 10.1212/wnl.0000000000201340
177. Juvela S, Poussa K, Lehto H, Porras M. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *Stroke*. 2013;44:2414-2421. doi: 10.1161/strokeaha.113.001838
178. Korja M, Lehto H, Juvela S. Lifelong rupture risk of intracranial aneurysms depends on risk factors: a prospective Finnish cohort study. *Stroke*. 2014;45:1958-1963. doi: 10.1161/strokeaha.114.005318
179. Meng H, Tutino VM, Xiang J, Siddiqui A. High WSS or low WSS? Complex interactions of hemodynamics with intracranial aneurysm initiation, growth, and rupture: toward a unifying hypothesis. *AJNR Am J Neuroradiol*. 2014;35:1254-1262. doi: 10.3174/ajnr.A3558
180. Staarmann B, Smith M, Prestigiacomo CJ. Shear stress and aneurysms: a review. *Neurosurg Focus*. 2019;47:E2. doi: 10.3171/2019.4.Focus19225
181. Frösen J, Cebral J, Robertson AM, Aoki T. Flow-induced, inflammation-mediated arterial wall remodeling in the formation and progression of intracranial aneurysms. *Neurosurg Focus*. 2019;47:E21. doi: 10.3171/2019.5.Focus19234
182. Baharoglu MI, Lauric A, Safain MG, Hippelheuser J, Wu C, Malek AM. Widening and high inclination of the middle cerebral artery bifurcation are associated with presence of aneurysms. *Stroke*. 2014;45:2649-2655. doi: 10.1161/strokeaha.114.005393
183. Zhang XJ, Gao BL, Hao WL, Wu SS, Zhang DH. Presence of Anterior Communicating Artery Aneurysm Is Associated With Age, Bifurcation Angle, and Vessel Diameter. *Stroke*. 2018;49:341-347. doi: 10.1161/strokeaha.117.019701
184. Canham PB, Finlay HM. Morphometry of medial gaps of human brain artery branches. *Stroke*. 2004;35:1153-1157. doi: 10.1161/01.STR.0000124926.76836.df
185. Aoki T, Kataoka H, Shimamura M, Nakagami H, Wakayama K, Moriwaki T, Ishibashi R, Nozaki K, Morishita R, Hashimoto N. NF-kappaB is a key mediator of cerebral aneurysm formation. *Circulation*. 2007;116:2830-2840. doi: 10.1161/circulationaha.107.728303

186. Tulamo R, Frösen J, Hernesniemi J, Niemelä M. Inflammatory changes in the aneurysm wall: a review. *J Neurointerv Surg*. 2018;10:i58-i67. doi: 10.1136/jnis.2009.002055.rep
187. Koseki H, Miyata H, Shimo S, Ohno N, Mifune K, Shimano K, Yamamoto K, Nozaki K, Kasuya H, Narumiya S, Aoki T. Two Diverse Hemodynamic Forces, a Mechanical Stretch and a High Wall Shear Stress, Determine Intracranial Aneurysm Formation. *Transl Stroke Res*. 2020;11:80-92. doi: 10.1007/s12975-019-0690-y
188. Aoki T, Kataoka H, Ishibashi R, Nozaki K, Egashira K, Hashimoto N. Impact of monocyte chemoattractant protein-1 deficiency on cerebral aneurysm formation. *Stroke*. 2009;40:942-951. doi: 10.1161/strokeaha.108.532556
189. Hasan D, Chalouhi N, Jabbour P, Hashimoto T. Macrophage imbalance (M1 vs. M2) and upregulation of mast cells in wall of ruptured human cerebral aneurysms: preliminary results. *J Neuroinflammation*. 2012;9:222. doi: 10.1186/1742-2094-9-222
190. Caird J, Napoli C, Taggart C, Farrell M, Bouchier-Hayes D. Matrix metalloproteinases 2 and 9 in human atherosclerotic and non-atherosclerotic cerebral aneurysms. *Eur J Neurol*. 2006;13:1098-1105. doi: 10.1111/j.1468-1331.2006.01469.x
191. Nakajima N, Nagahiro S, Sano T, Satomi J, Satoh K. Phenotypic modulation of smooth muscle cells in human cerebral aneurysmal walls. *Acta Neuropathol*. 2000;100:475-480. doi: 10.1007/s004010000220
192. Robertson AM, Duan X, Aziz KM, Hill MR, Watkins SC, Cebral JR. Diversity in the Strength and Structure of Unruptured Cerebral Aneurysms. *Ann Biomed Eng*. 2015;43:1502-1515. doi: 10.1007/s10439-015-1252-4
193. Harada K, Fukuyama K, Shirouzu T, Ichinose M, Fujimura H, Kakumoto K, Yamanaga Y. Prevalence of unruptured intracranial aneurysms in healthy asymptomatic Japanese adults: differences in gender and age. *Acta Neurochir (Wien)*. 2013;155:2037-2043. doi: 10.1007/s00701-013-1841-7
194. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry*. 2007;78:1365-1372. doi: 10.1136/jnnp.2007.117655
195. Zuurbier CCM, Molenberg R, Mensing LA, Wermer MJH, Juvela S, Lindgren AE, Jääskeläinen JE, Koivisto T, Yamazaki T, Uyttenboogaart M, et al. Sex Difference and Rupture Rate of Intracranial Aneurysms: An Individual Patient Data Meta-Analysis. *Stroke*. 2022;53:362-369. doi: 10.1161/strokeaha.121.035187
196. Ding C, Toll V, Ouyang B, Chen M. Younger age of menopause in women with cerebral aneurysms. *J Neurointerv Surg*. 2013;5:327-331. doi: 10.1136/neurintsurg-2012-010364
197. Fuentes AM, Stone McGuire L, Amin-Hanjani S. Sex Differences in Cerebral Aneurysms and Subarachnoid Hemorrhage. *Stroke*. 2022;53:624-633. doi: 10.1161/strokeaha.121.037147
198. Räisänen S, Frösen J, Kurki MI, Huttunen T, Huttunen J, Koivisto T, Helin K, von Und Zu Fraunberg M, Jääskeläinen JE, Lindgren AE. Impact of Young Age on the Presentation of Saccular Intracranial Aneurysms: Population-Based Analysis of 4082 Patients. *Neurosurgery*. 2018;82:815-823. doi: 10.1093/neuros/nyx305
199. Lindgren AE, Räisänen S, Björkman J, Tattari H, Huttunen J, Huttunen T, Kurki MI, Frösen J, Koivisto T, Jääskeläinen JE, von Und Zu Fraunberg M. De Novo Aneurysm Formation in Carriers of Saccular Intracranial Aneurysm Disease in Eastern Finland. *Stroke*. 2016;47:1213-1218. doi: 10.1161/strokeaha.115.012573
200. Bakker MK, van der Spek RAA, van Rheenen W, Morel S, Bourcier R, Hostettler IC, Alg VS, van Eijk KR, Koido M, Akiyama M, et al. Genome-wide association study of intracranial aneurysms identifies 17 risk loci and genetic overlap with clinical risk factors. *Nat Genet*. 2020;52:1303-1313. doi: 10.1038/s41588-020-00725-7
201. Korja M, Silventoinen K, McCarron P, Zdravkovic S, Skytthe A, Haapanen A, de Faire U, Pedersen NL, Christensen K, Koskenvuo M, Kaprio J. Genetic epidemiology of spontaneous

subarachnoid hemorrhage: Nordic Twin Study. *Stroke*. 2010;41:2458-2462. doi: 10.1161/strokeaha.110.586420
202. Schievink WI, Schaid DJ, Michels VV, Piepgras DG. Familial aneurysmal subarachnoid hemorrhage: a community-based study. *J Neurosurg*. 1995;83:426-429. doi: 10.3171/jns.1995.83.3.0426
203. Bromberg JE, Rinkel GJ, Algra A, Greebe P, van Duyn CM, Hasan D, Limburg M, ter Berg HW, Wijdicks EF, van Gijn J. Subarachnoid haemorrhage in first and second degree relatives of patients with subarachnoid haemorrhage. *Bmj*. 1995;311:288-289. doi: 10.1136/bmj.311.7000.288
204. Broderick JP, Brown RD, Jr., Sauerbeck L, Hornung R, Huston J, 3rd, Woo D, Anderson C, Rouleau G, Kleindorfer D, Flaherty ML, et al. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. *Stroke*. 2009;40:1952-1957. doi: 10.1161/strokeaha.108.542571
205. Mensing LA, Greving JP, Verhoeff TA, Rinkel GJE, Ruigrok YM. Comparison of Rupture Risk of Intracranial Aneurysms Between Familial and Sporadic Patients. *Stroke*. 2019;50:1380-1383. doi: 10.1161/strokeaha.118.023783
206. Slot EMH, Rinkel GJE, Algra A, Ruigrok YM. Patient and aneurysm characteristics in familial intracranial aneurysms. A systematic review and meta-analysis. *PLoS One*. 2019;14:e0213372. doi: 10.1371/journal.pone.0213372
207. Kim K, Drummond I, Ibraghimov-Beskrovnaya O, Klinger K, Arnaout MA. Polycystin 1 is required for the structural integrity of blood vessels. *Proc Natl Acad Sci U S A*. 2000;97:1731-1736. doi: 10.1073/pnas.040550097
208. Zhou Z, Xu Y, Delcourt C, Shan J, Li Q, Xu J, Hackett ML. Is Regular Screening for Intracranial Aneurysm Necessary in Patients with Autosomal Dominant Polycystic Kidney Disease? A Systematic Review and Meta-analysis. *Cerebrovasc Dis*. 2017;44:75-82. doi: 10.1159/000476073
209. Kim ST, Brinjikji W, Kallmes DF. Prevalence of Intracranial Aneurysms in Patients with Connective Tissue Diseases: A Retrospective Study. *AJNR Am J Neuroradiol*. 2016;37:1422-1426. doi: 10.3174/ajnr.A4718
210. Bober MB, Khan N, Kaplan J, Lewis K, Feinstein JA, Scott CI, Jr., Steinberg GK. Majewski osteodysplastic primordial dwarfism type II (MOPD II): expanding the vascular phenotype. *Am J Med Genet A*. 2010;152a:960-965. doi: 10.1002/ajmg.a.33252
211. Laarman MD, Vermunt MW, Kleinloog R, de Boer-Bergsma JJ, Brain Bank N, Rinkel GJE, Creyghton MP, Mokry M, Bakkers J, Ruigrok YM. Intracranial Aneurysm-Associated Single-Nucleotide Polymorphisms Alter Regulatory DNA in the Human Circle of Willis. *Stroke*. 2018;49:447-453. doi: 10.1161/strokeaha.117.018557
212. Poppenberg KE, Jiang K, Tso MK, Snyder KV, Siddiqui AH, Kolega J, Jarvis JN, Meng H, Tutino VM. Epigenetic landscapes suggest that genetic risk for intracranial aneurysm operates on the endothelium. *BMC Med Genomics*. 2019;12:149. doi: 10.1186/s12920-019-0591-7
213. Bakker MK, Ruigrok YM. Genetics of Intracranial Aneurysms. *Stroke*. 2021;52:3004-3012. doi: 10.1161/strokeaha.120.032621
214. Etminan N, Dörfler A, Steinmetz H. Unruptured Intracranial Aneurysms- Pathogenesis and Individualized Management. *Dtsch Arztebl Int*. 2020;117:235-242. doi: 10.3238/arztebl.2020.0235
215. Sun X, Liu B, Chen Y, Lv L, Ye D, Mao Y. Modifiable risk factors for intracranial aneurysms: Evidence from genetic studies. *Int J Stroke*. 2022;17:1107-1113. doi: 10.1177/17474930211065640
216. Karhunen V, Bakker MK, Ruigrok YM, Gill D, Larsson SC. Modifiable Risk Factors for Intracranial Aneurysm and Aneurysmal Subarachnoid Hemorrhage: A Mendelian Randomization Study. *J Am Heart Assoc*. 2021;10:e022277. doi: 10.1161/jaha.121.022277
217. Huttunen T, von und zu Fraunberg M, Frösen J, Lehecka M, Tromp G, Helin K, Koivisto T, Rinne J, Ronkainen A, Hernesniemi J, Jääskeläinen JE. Saccular intracranial aneurysm disease: distribution of site, size, and age suggests different etiologies for aneurysm formation and rupture

in 316 familial and 1454 sporadic eastern Finnish patients. *Neurosurgery*. 2010;66:631-638; discussion 638. doi: 10.1227/01.Neu.0000367634.89384.4b
218. Lindgren AE, Kurki MI, Riihinen A, Koivisto T, Ronkainen A, Rinne J, Hernesniemi J, Eriksson JG, Jääskeläinen JE, von und zu Fraunberg M. Hypertension predisposes to the formation of saccular intracranial aneurysms in 467 unruptured and 1053 ruptured patients in Eastern Finland. *Ann Med*. 2014;46:169-176. doi: 10.3109/07853890.2014.883168
219. Brown RD, Jr., Broderick JP. Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening. *Lancet Neurol*. 2014;13:393-404. doi: 10.1016/s1474-4422(14)70015-8
220. Backes D, Rinkel GJ, Laban KG, Algra A, Vergouwen MD. Patient- and Aneurysm-Specific Risk Factors for Intracranial Aneurysm Growth: A Systematic Review and Meta-Analysis. *Stroke*. 2016;47:951-957. doi: 10.1161/strokeaha.115.012162
221. Vlak MH, Rinkel GJ, Greebe P, Algra A. Independent risk factors for intracranial aneurysms and their joint effect: a case-control study. *Stroke*. 2013;44:984-987. doi: 10.1161/strokeaha.111.000329
222. Ogilvy CS, Gomez-Paz S, Kicielinski KP, Salem MM, Akamatsu Y, Waqas M, Rai HH, Catapano JS, Muram S, Elghareeb M, et al. Cigarette smoking and risk of intracranial aneurysms in middle-aged women. *J Neurol Neurosurg Psychiatry*. 2020;91:985-990. doi: 10.1136/jnnp-2020-323753
223. Can A, Castro VM, Ozdemir YH, Dagen S, Yu S, Dligach D, Finan S, Gainer V, Shadick NA, Murphy S, et al. Association of intracranial aneurysm rupture with smoking duration, intensity, and cessation. *Neurology*. 2017;89:1408-1415. doi: 10.1212/wnl.0000000000004419
224. Feigin VL, Rinkel GJ, Lawes CM, Algra A, Bennett DA, van Gijn J, Anderson CS. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke*. 2005;36:2773-2780. doi: 10.1161/01.STR.0000190838.02954.e8
225. Lindbohm JV, Rautalin I, Jousilahti P, Salomaa V, Kaprio J, Korja M. Physical activity associates with subarachnoid hemorrhage risk- a population-based long-term cohort study. *Sci Rep*. 2019;9:9219. doi: 10.1038/s41598-019-45614-0
226. Sundström J, Söderholm M, Söderberg S, Alfredsson L, Andersson M, Bellocco R, Björck M, Broberg P, Eriksson M, Eriksson M, et al. Risk factors for subarachnoid haemorrhage: a nationwide cohort of 950 000 adults. *Int J Epidemiol*. 2019;48:2018-2025. doi: 10.1093/ije/dyz163
227. Larsson SC, Bäck M, Rees JMB, Mason AM, Burgess S. Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomization study. *Eur Heart J*. 2020;41:221-226. doi: 10.1093/eurheartj/ehz388
228. Frösen J, Tulamo R, Heikura T, Sammalkorpi S, Niemelä M, Hernesniemi J, Levonen AL, Hörkkö S, Ylä-Herttuala S. Lipid accumulation, lipid oxidation, and low plasma levels of acquired antibodies against oxidized lipids associate with degeneration and rupture of the intracranial aneurysm wall. *Acta Neuropathol Commun*. 2013;1:71. doi: 10.1186/2051-5960-1-71
229. Ollikainen E, Tulamo R, Lehti S, Lee-Rueckert M, Hernesniemi J, Niemelä M, Ylä-Herttuala S, Kovanen PT, Frösen J. Smooth Muscle Cell Foam Cell Formation, Apolipoproteins, and ABCA1 in Intracranial Aneurysms: Implications for Lipid Accumulation as a Promoter of Aneurysm Wall Rupture. *J Neuropathol Exp Neurol*. 2016;75:689-699. doi: 10.1093/jnen/nlw041
230. Frösen J, Tulamo R, Paetau A, Laaksamo E, Korja M, Laakso A, Niemelä M, Hernesniemi J. Saccular intracranial aneurysm: pathology and mechanisms. *Acta Neuropathol*. 2012;123:773-786. doi: 10.1007/s00401-011-0939-3
231. Gade PS, Tulamo R, Lee KW, Mut F, Ollikainen E, Chuang CY, Jae Chung B, Niemelä M, Rezai Jahromi B, Aziz K, et al. Calcification in Human Intracranial Aneurysms Is Highly Prevalent and Displays Both Atherosclerotic and Nonatherosclerotic Types. *Arterioscler Thromb Vasc Biol*. 2019;39:2157-2167. doi: 10.1161/atvbaha.119.312922

232. Kamphuis MJ, van der Kamp LT, Lette E, Rinkel GJE, Vergouwen MDI, van der Schaaf IC, de Jong PA, Ruigrok YM. Intracranial arterial calcification in patients with unruptured and ruptured intracranial aneurysms. *Eur Radiol*. 2024;34:7517-7525. doi: 10.1007/s00330-024-10789-2
233. Etminan N, Rinkel GJ. Unruptured intracranial aneurysms: development, rupture and preventive management. *Nat Rev Neurol*. 2016;12:699-713. doi: 10.1038/nrneurol.2016.150
234. Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, Hashimoto N, Nakayama T, Sakai M, Teramoto A, Tominari S, Yoshimoto T. The natural course of unruptured cerebral aneurysms in a Japanese cohort. *N Engl J Med*. 2012;366:2474-2482. doi: 10.1056/NEJMoa1113260
235. Wiebers DO, Whisnant JP, Huston J, 3rd, Meissner I, Brown RD, Jr., Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet*. 2003;362:103-110. doi: 10.1016/s0140-6736(03)13860-3
236. Webb M, Fischer V, Farrell R, Towne J, Birnbaum L, Rodriguez P, Mascitelli J. The majority of ruptured aneurysms are small with low rupture risk scores. *J Clin Neurosci*. 2022;103:148-152. doi: 10.1016/j.jocn.2022.06.015
237. Wang Y, Cheng M, Liu S, Xie G, Liu L, Wu X, Malhotra A, Mossa-Basha M, Zhu C. Shape related features of intracranial aneurysm are associated with rupture status in a large Chinese cohort. *J Neurointerv Surg*. 2022;14:252-256. doi: 10.1136/neurintsurg-2021-017452
238. Waqas M, Chin F, Rajabzadeh-Oghaz H, Gong AD, Rai HH, Mokin M, Vakharia K, Dossani RH, Meng H, Snyder KV, et al. Size of ruptured intracranial aneurysms: a systematic review and meta-analysis. *Acta Neurochir (Wien)*. 2020;162:1353-1362. doi: 10.1007/s00701-020-04291-z
239. Villablanca JP, Duckwiler GR, Jahan R, Tateshima S, Martin NA, Frazee J, Gonzalez NR, Sayre J, Vinuela FV. Natural history of asymptomatic unruptured cerebral aneurysms evaluated at CT angiography: growth and rupture incidence and correlation with epidemiologic risk factors. *Radiology*. 2013;269:258-265. doi: 10.1148/radiol.13121188
240. Feng J, Tang Y, You W, Jiang Y, Xu Z, Zhao Y, Liu X, Lv J, Liu P, Wei H, et al. Risk analysis of intracranial aneurysm rupture based on the arterial segment of origin. *Front Neurol*. 2024;15:1339144. doi: 10.3389/fneur.2024.1339144
241. Korja M, Kivisaari R, Rezai Jahromi B, Lehto H. Size and location of ruptured intracranial aneurysms: consecutive series of 1993 hospital-admitted patients. *J Neurosurg*. 2017;127:748-753. doi: 10.3171/2016.9.Jns161085
242. Diagbouga MR, Morel S, Bijlenga P, Kwak BR. Role of hemodynamics in initiation/growth of intracranial aneurysms. *Eur J Clin Invest*. 2018;48:e12992. doi: 10.1111/eci.12992
243. Sanchez S, Hickerson M, Patel RR, Ghazaleh D, Tarchand R, Paranjape GS, Pope H, Ortega-Gutierrez S, Pederson JM, Hasan D, et al. Morphological Characteristics of Ruptured Brain Aneurysms: A Systematic Literature Review and Meta-Analysis. *Stroke: Vascular and Interventional Neurology*. 2023;3:e000707. doi: doi:10.1161/SVIN.122.000707
244. Dhar S, Tremmel M, Mocco J, Kim M, Yamamoto J, Siddiqui AH, Hopkins LN, Meng H. Morphology parameters for intracranial aneurysm rupture risk assessment. *Neurosurgery*. 2008;63:185-196; discussion 196-187. doi: 10.1227/01.Neu.0000316847.64140.81
245. Kleinloog R, de Mul N, Verweij BH, Post JA, Rinkel GJE, Ruigrok YM. Risk Factors for Intracranial Aneurysm Rupture: A Systematic Review. *Neurosurgery*. 2018;82:431-440. doi: 10.1093/neuros/nyx238
246. Lindgren AE, Koivisto T, Björkman J, von Und Zu Fraunberg M, Helin K, Jääskeläinen JE, Frösen J. Irregular Shape of Intracranial Aneurysm Indicates Rupture Risk Irrespective of Size in a Population-Based Cohort. *Stroke*. 2016;47:1219-1226. doi: 10.1161/strokeaha.115.012404
247. Falk Delgado A, Andersson T, Falk Delgado A. Clinical outcome after surgical clipping or endovascular coiling for cerebral aneurysms: a pragmatic meta-analysis of randomized and non-randomized trials with short- and long-term follow-up. *J Neurointerv Surg*. 2017;9:264-277. doi: 10.1136/neurintsurg-2016-012292

248. Bor AS, Rinkel GJ, Adami J, Koffijberg H, Ekbom A, Buskens E, Blomqvist P, Granath F. Risk of subarachnoid haemorrhage according to number of affected relatives: a population based case-control study. *Brain*. 2008;131:2662-2665. doi: 10.1093/brain/awn187
249. Bor AS, Rinkel GJ, van Norden J, Wermer MJ. Long-term, serial screening for intracranial aneurysms in individuals with a family history of aneurysmal subarachnoid haemorrhage: a cohort study. *Lancet Neurol*. 2014;13:385-392. doi: 10.1016/s1474-4422(14)70021-3
250. Greving JP, Wermer MJ, Brown RD, Jr., Morita A, Juvela S, Yonekura M, Ishibashi T, Torner JC, Nakayama T, Rinkel GJ, Algra A. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol*. 2014;13:59-66. doi: 10.1016/s1474-4422(13)70263-1
251. Pagiola I, Mihalea C, Caroff J, Ikka L, Chalumeau V, Iacobucci M, Ozanne A, Gallas S, Marques M, Nalli D, et al. The PHASES score: To treat or not to treat? Retrospective evaluation of the risk of rupture of intracranial aneurysms in patients with aneurysmal subarachnoid hemorrhage. *J Neuroradiol*. 2020;47:349-352. doi: 10.1016/j.neurad.2019.06.003
252. Foreman PM, Hendrix P, Harrigan MR, Fisher WS, 3rd, Vyas NA, Lipsky RH, Walters BC, Tubbs RS, Shoja MM, Griessenauer CJ. PHASES score applied to a prospective cohort of aneurysmal subarachnoid hemorrhage patients. *J Clin Neurosci*. 2018;53:69-73. doi: 10.1016/j.jocn.2018.04.014
253. Rutledge C, Jonzzon S, Winkler EA, Raper D, Lawton MT, Abla AA. Small Aneurysms with Low PHASES Scores Account for Most Subarachnoid Hemorrhage Cases. *World Neurosurg*. 2020;139:e580-e584. doi: 10.1016/j.wneu.2020.04.074
254. Backes D, Rinkel GJE, Greving JP, Velthuis BK, Murayama Y, Takao H, Ishibashi T, Igase M, terBrugge KG, Agid R, et al. ELAPSS score for prediction of risk of growth of unruptured intracranial aneurysms. *Neurology*. 2017;88:1600-1606. doi: 10.1212/wnl.0000000000003865
255. Sturiale CL, Stumpo V, Ricciardi L, Trevisi G, Valente I, D'Arrigo S, Latour K, Barbone P, Albanese A. Retrospective application of risk scores to ruptured intracranial aneurysms: would they have predicted the risk of bleeding? *Neurosurg Rev*. 2021;44:1655-1663. doi: 10.1007/s10143-020-01352-w
256. Juvela S. Scoring of Growth of Unruptured Intracranial Aneurysms. *J Clin Med*. 2020;9. doi: 10.3390/jcm9103339
257. Etminan N, Brown RD, Jr., Beseoglu K, Juvela S, Raymond J, Morita A, Torner JC, Derdeyn CP, Raabe A, Mocco J, et al. The unruptured intracranial aneurysm treatment score: a multidisciplinary consensus. *Neurology*. 2015;85:881-889. doi: 10.1212/wnl.0000000000001891
258. Molenberg R, Aalbers MW, Mazuri A, Luijckx GJ, Metzemaekers JDM, Groen RJM, Uyttenboogaart M, van Dijk JMC. The Unruptured Intracranial Aneurysm Treatment Score as a predictor of aneurysm growth or rupture. *Eur J Neurol*. 2021;28:837-843. doi: 10.1111/ene.14636
259. Hernández-Durán S, Mielke D, Rohde V, Malinova V. Is the unruptured intracranial aneurysm treatment score (UIATS) sensitive enough to detect aneurysms at risk of rupture? *Neurosurg Rev*. 2021;44:987-993. doi: 10.1007/s10143-020-01246-x
260. [database online]. 2013.
261. Foley MP, Tubassam M, Walsh SR. An audit of secondary prevention for peripheral arterial disease in primary care - scope for improved collaboration between vascular surgery and general practitioners. *Ir J Med Sci*. 2023;192:3007-3010. doi: 10.1007/s11845-023-03362-1
262. Diehm C, Allenberg JR, Pittrow D, Mahn M, Tepohl G, Haberl RL, Darius H, Burghaus I, Trampisch HJ. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation*. 2009;120:2053-2061. doi: 10.1161/circulationaha.109.865600
263. McDermott MM, Liu K, Criqui MH, Ruth K, Goff D, Saad MF, Wu C, Homma S, Sharrett AR. Ankle-brachial index and subclinical cardiac and carotid disease: the multi-ethnic study of atherosclerosis. *Am J Epidemiol*. 2005;162:33-41. doi: 10.1093/aje/kwi167

264. Gupta DK, Skali H, Claggett B, Kasabov R, Cheng S, Shah AM, Loehr LR, Heiss G, Nambi V, Aguilar D, et al. Heart failure risk across the spectrum of ankle-brachial index: the ARIC study (Atherosclerosis Risk In Communities). *JACC Heart Fail*. 2014;2:447-454. doi: 10.1016/j.jchf.2014.05.008
265. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. *Am Heart J*. 2002;143:961-965. doi: 10.1067/mhj.2002.122871
266. Menke A, Muntner P, Wildman RP, Dreisbach AW, Raggi P. Relation of borderline peripheral arterial disease to cardiovascular disease risk. *Am J Cardiol*. 2006;98:1226-1230. doi: 10.1016/j.amjcard.2006.05.056
267. Kajikawa M, Maruhashi T, Iwamoto Y, Iwamoto A, Matsumoto T, Hidaka T, Kihara Y, Chayama K, Nakashima A, Goto C, et al. Borderline ankle-brachial index value of 0.91-0.99 is associated with endothelial dysfunction. *Circ J*. 2014;78:1740-1745. doi: 10.1253/circj.cj-14-0165
268. Wattanakit K, Folsom AR, Duprez DA, Weatherley BD, Hirsch AT. Clinical significance of a high ankle-brachial index: insights from the Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis*. 2007;190:459-464. doi: 10.1016/j.atherosclerosis.2006.02.039
269. Hoek AG, Zwakenberg SR, Elders PJM, de Jong PA, Spiering W, Bartstra JW, Doesburg T, van der Heijden AA, van der Schouw YT, Beulens JWJ. An elevated ankle-brachial index is not a valid proxy for peripheral medial arterial calcification. *Atherosclerosis*. 2021;323:13-19. doi: 10.1016/j.atherosclerosis.2021.03.010
270. Ix JH, Miller RG, Criqui MH, Orchard TJ. Test characteristics of the ankle-brachial index and ankle-brachial difference for medial arterial calcification on X-ray in type 1 diabetes. *J Vasc Surg*. 2012;56:721-727. doi: 10.1016/j.jvs.2012.02.042
271. Young MJ, Adams JE, Anderson GF, Boulton AJ, Cavanagh PR. Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. *Diabetologia*. 1993;36:615-621. doi: 10.1007/bf00404070
272. Hashimoto J. Pulse pressure amplification as a hemodynamic predictor of cardiovascular disease. *Hypertens Res*. 2024;47:3270-3272. doi: 10.1038/s41440-024-01880-8
273. Lilly SM, Jacobs DR, Jr., Kronmal R, Bluemke DA, Criqui M, Lima J, Allison M, Duprez D, Segers P, Chirinos JA. Arterial compliance across the spectrum of ankle-brachial index: the Multiethnic Study of Atherosclerosis. *Atherosclerosis*. 2014;233:691-696. doi: 10.1016/j.atherosclerosis.2014.01.029
274. Cocciolone AJ, Hawes JZ, Staiculescu MC, Johnson EO, Murshed M, Wagenseil JE. Elastin, arterial mechanics, and cardiovascular disease. *Am J Physiol Heart Circ Physiol*. 2018;315:H189-h205. doi: 10.1152/ajpheart.00087.2018
275. Tabara Y, Igase M, Kido T, Ochi N, Miki T, Kohara K. Composition of lower extremity in relation to a high ankle-brachial index. *J Hypertens*. 2009;27:167-173. doi: 10.1097/HJH.0b013e328314b821
276. Rantasalo V, Gunn J, Kiviniemi T, Hirvonen J, Saarenpää I, Kivelev J, Rahi M, Lassila E, Rinne J, Laukka D. Intracranial aneurysm is predicted by abdominal aortic calcification index: A retrospective case-control study. *Atherosclerosis*. 2021;334:30-38. doi: 10.1016/j.atherosclerosis.2021.08.027
277. Aboyans V, McClelland RL, Allison MA, McDermott MM, Blumenthal RS, Macura K, Criqui MH. Lower extremity peripheral artery disease in the absence of traditional risk factors. The Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2011;214:169-173. doi: 10.1016/j.atherosclerosis.2010.10.011
278. Qu B, Liu Q, Li J. Systematic Review of Association Between Low Ankle-Brachial Index and All-Cause Cardiovascular, or Non-cardiovascular Mortality. *Cell Biochem Biophys*. 2015;73:571-575. doi: 10.1007/s12013-015-0582-z
279. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, 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*. 2008;337:a1840. doi: 10.1136/bmj.a1840

280. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandercock PA, Fox KA, Lowe GD, Murray GD. 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. doi: 10.1001/jama.2010.221
281. Hudson JS, Marincovich AJ, Roa JA, Zanaty M, Samaniego EA, Hasan DM. Aspirin and Intracranial Aneurysms. *Stroke*. 2019;50:2591-2596. doi: 10.1161/strokeaha.119.026094
282. Vergouwen MD, Rinkel GJ, Algra A, Fiehler J, Steinmetz H, Vajkoczy P, Rutten FH, Luntz S, Hänggi D, Etminan N. Prospective Randomized Open-label Trial to evaluate risk faCTor management in patients with Unruptured intracranial aneurysms: Study protocol. *Int J Stroke*. 2018;13:992-998. doi: 10.1177/1747493018790033

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Painosalama, Turku, Finland 2025

ISBN 978-952-02-0319-1 (PRINT)
ISBN 978-952-02-0320-7 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)