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To Whom it May Concern

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ABSTRACT

Peripheral artery disease (PAD) causes increased all-cause and cardiovascular (CV) mortality. These increases have been associated with abnormal ankle-brachial indices and the extent of atherosclerotic lesions as measured by radiological imaging. Reported associations of outcome in regard to systolic toe pressure (TP) are scarce, and those associations in regard to lesion distribution have been ambiguous. This thesis has two aims. First, to clarify the relationship of TP with outcome in patients with symptomatic PAD. Second, to clarify the association of anatomical distribution and extensiveness of angiographically detected lower extremity atherosclerotic lesions with outcome in the same patients.

This thesis retrospectively reviews 887 patients whom underwent digital subtraction angiography (DSA) for the following: peripheral pressure measurements, DSA images and causes of death. Within a median 4.6 years follow-up, almost half of the patients had died, and of these deaths 60% had been due to CV causes. Angiographic lesion distribution, severity and TP were independently associated with increased all-cause and CV mortality.

A predominantly or exclusively crural distribution of atherosclerotic lesions in the lower extremities and widespread lesions in the crural arteries predicted increased CV and all-cause mortality in symptomatic PAD patients undergoing DSA. Estimated cumulative survival and freedom from CV death could be stratified according to TP categories < 30 mmHg, 30–49 mmHg and ≥ 50 mmHg in the affected lower extremity. TP < 30 mmHg was independently associated with increased all-cause and CV mortality and decreased amputation-free survival. Bilaterally low TP was associated with a particularly poor outcome.

KEYWORDS: Peripheral artery disease, angiography, toe pressure, mortality

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TIIVISTELMÄ

Alaraajojen tukkiva valtimotauti johtaa lisääntyneeseen kokonais- ja kardiovaskulaarikuolleisuuteen. Poikkeavan nilkka-olkavarsipaineindeksin ja kuvantamistutkimuksissa määritetyn tautimuutosten laajuuden on osoitettu liittyvän tähän. Lopputuleman yhteyksiä systoliseen varvaspaineeseen on raportoitu niukalti ja sen raportoidut yhteydet tautimuutosten sijainnin jakautumiseen ovat ristiriitaisia. Tämän väitöskirjan tarkoitus on selventää varvaspaineen ja angiografisten tautimuutosten anatomisen jakauman sekä laajuuden yhteyttä oireista perifeeristä valtimokovettumatautia sairastavien potilaiden ennusteeseen.

Väitöskirjassa tarkasteltiin retrospektiivisesti perifeerisiä valtimopainemittauksia, varjoainekuvia ja kuolinsyitä 887:lla oireisella alaraajojen tukkivaa valtimotautia sairastavalla potilaalla, joille tehtiin alaraajojen varjoainekuvaus. Keskimäärin 4,6 vuoden seurannan aikana lähes puolet potilaista kuoli, joista 60 % kardiovaskulaarisista syistä johtuen. Angiografisten tautimuutosten sijainnin jakautuminen ja vaikeusaste, sekä varvaspaine assosioituivat itsenäisesti lisääntyneeseen kokonais- ja kardiovaskulaarikuolleisuuteen.

Valtaosin tai yksinomaan säären tasoon paikantuvat valtimotautimuutokset ja laaja-alainen säärivaltimoiden tauti ennustivat lisääntynyttä kardiovaskulaari- ja kokonaiskuolleisuutta oireista alaraajojen valtimokovettumatautia sairastavilla potilailla, joille tehtiin alaraajojen varjoainekuvaus. Kumulatiivinen elossaolo ja kardiovaskulaarikuolemalta välttyminen voitiin ryhmittää oireisen alaraajan varvaspaineluokkien < 30 mmHg, 30–49 mmHg ja ≥ 50 mmHg perusteella. Varvaspaine < 30 mmHg oli itsenäinen riskitekijä lisääntyneelle kokonais- ja kardiovaskulaarikuolleisuudelle. Molemminpuolisesti alhaisiin varvaspaineisiin liittyi erityisen huono ennuste.

AVAINSANAT: Alaraajojen tukkiva valtimotauti, angiografia, varvaspaine, kuolleisuus

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Abbreviations and Definitions

ABI	Ankle-brachial index
ACC	American College of Cardiology
AFS	Amputation-free survival
AHA	American Heart Association
ALI	Acute limb ischaemia
AP	Ankle pressure
ARIC	Atherosclerosis Risk in Communities (study)
ARS	Anatomic runoff score
BARI 2D	Bypass Angioplasty Revascularization Investigation 2 Diabetes (trial)
BASIL	Bypass versus Angioplasty in Severe Ischaemia of the Leg (trial)
CABG	Coronary artery bypass grafting
CAC	Coronary artery calcification
CAD	Coronary artery disease
CHS	Cardiovascular Health Study (study)
CI	Confidence interval
CIx	Crural Index
CLI	Critical limb ischaemia
CLTI	Chronic limb-threatening ischaemia
CL_TP	Contralateral toe pressure
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies (trial)
COPART	Cohorte de Patients Artériopathes (registry)
COPD	Chronic obstructive pulmonary disease
CT(A)	Computed tomography (angiography)
CV	Cardiovascular
CVD	Cardiovascular disease
(D)DUS	(Duplex) doppler ultrasound
DSA	Digital subtraction angiography
EAS	Edinburgh Artery Study

ESRD	End-stage renal disease
FCD	Freedom from cardiovascular death
GLASS	Global limb anatomic staging system
HR	Hazard ratio
IC	Intermittent claudication
IMPACT-ABI	Impressive Predictive Value of Ankle-Brachial Index for Very Long Term Outcome in Patients with Cardiovascular Disease (study)
IN.PACT DEEP	Randomized IN.PACT Amphirion Drug-Coated Balloon vs. Standard Percutaneous Transluminal Angioplasty for the Treatment of Below-the-Knee Critical Limb Ischaemia (trial)
IP_TP	Ipsilateral toe pressure
IWGDF	International Working Group on the Diabetic Foot
LLAC	Lower limb arterial calcification
LV-PAD	Large-vessel peripheral artery disease
MAC	Medial arterial calcification
MACE	Major adverse cardiovascular event
MALE	Major adverse limb event
MI	Myocardial infarction
OR	Odds ratio
OS	Overall survival
PAD	Peripheral artery disease
PCA	Poorly compressible arteries
REACH	Reduction of Atherothrombosis for Continued Health (registry)
ROC	Receiver operating characteristic
RR	Relative risk
SD	Standard deviation
SE	Standard error
SV-PAD	Small-vessel peripheral artery disease
SVS	Society for Vascular Surgery
TAC	Thoracic aortic calcium
TASC	Trans-Atlantic Inter-Society Consensus
TBI	Toe-brachial index
$TcPO_2$	Transcutaneous oxygen pressure
TIA	Transient ischaemic attack
TP	Toe pressure
WIfI	Wound, Ischaemia, foot Infection

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 Jalkanen JM, Wickstrom JE, Venermo M, Hakovirta HH. The extent of atherosclerotic lesions in crural arteries predicts survival of patients with lower limb peripheral artery disease. *Atherosclerosis*, 2016; 251: 328–333.

II Wickstrom JE, Jalkanen JM, Venermo M, Hakovirta HH. Crural Index and extensive atherosclerosis of crural vessels are associated with long-term cardiovascular mortality in patients with symptomatic peripheral artery disease. *Atherosclerosis*, 2017; 264: 44–50.

III Wickstrom 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.

IV Wickstrom 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.

1 Introduction

Arteriosclerosis is defined as the degenerative loss of elasticity and thickening of the arterial walls through the loss of elastin fibres and collagenous remodelling – a condition inevitably associated with aging.[1] Arteriosclerosis often coexists with atherosclerosis: a pathological process of lipid plaque accumulation within the inner arterial wall driven by mechanical, chemical or inflammatory irritation.[2] Peripheral artery disease (PAD) is defined as the atherosclerotic narrowing of the arteries supplying blood to the extremities, which most commonly affects the lower limbs,[3] although the term 'lower extremity artery disease' (LEAD) is increasingly used in Europe when exclusively referring to lower limb PAD.[4] PAD affects over 200 million people worldwide with an increasing incidence and prevalence, particularly among women in middle and low-income countries. The prevalence of PAD increases with age: e.g. 5% for 45–49 year-olds and 18% for 85–89 year-olds in high-income countries.[5] Risk factors for PAD, besides increasing age, include the male sex, smoking, diabetes, hypertension, dyslipidaemia, chronic renal insufficiency and African ethnicity.[6] Increasing age, smoking and diabetes are most predictive of disease progression.[7,8]

Current guidelines by the European Society for Vascular Surgery, the European Society of Cardiology, the American Heart Association (AHA), the American College of Cardiology (ACC) and Society for Vascular Surgery (SVS) recommend the use of Ankle-brachial index (ABI) for the diagnosis and surveillance of PAD. ABI is the ratio between systolic ankle pressure and the highest systolic brachial pressure. Values ≤ 0.9 and > 1.40 or ≥ 1.40 are considered abnormal. The recommendation from the International Working Group on the Diabetic Foot (IWGDF) considers ABI < 0.9 and ≥ 1.3 to be abnormal. AHA/ACC, SVS and IWGDF also recommend using toe-brachial index (TBI) as either an alternative or complementary to ABI. TBI is calculated by dividing the systolic toe pressure by the highest systolic brachial pressure. TBI ≤ 0.70 is considered abnormal.[4,9–11]

Typical manifestations of symptomatic lower-limb PAD are functional impairment in the form of intermittent claudication (IC) or critical limb ischaemia (CLI), as classified by Fontaine (Table 1) and Rutherford (Table 2).[12,13] In order to emphasise the chronic nature of PAD and to differentiate CLI from acute limb ischaemia (ALI), the recommended term chronic limb-threatening ischaemia (CLTI)

has largely replaced CLI in scientific publications, and is thus used throughout this thesis.[14] Claudication is age-dependently present in 1–6% of the general population. Overall mortality, and cardiovascular (CV) mortality in particular, are higher in patients with claudication than in patients with asymptomatic PAD. Some 20% of individuals with claudication experience a clinical deterioration over a period of 5 years, with two-thirds developing worsening symptoms and one-third developing CLTI. The risk of amputation in IC patients has in the past been estimated to be low, but this view has more recently been challenged with a reported lifetime risk for amputation of up to 20%.[15,16]

Table 1. Fontaine classification.

Grade	Symptoms
Stage I	Asymptomatic, incomplete blood vessel obstruction
Stage II	Mild claudication pain in limb
Stage IIA	Claudication at a distance > 200 m
Stage IIB	Claudication at a distance < 200 m
Stage III	Rest pain, mostly in the feet
Stage IV	Necrosis and/or gangrene in the limb

Adapted from: Fontaine, Kim et Kieny, 1954.

Table 2. Rutherford classification for chronic limb ischaemia.

Grade	Category	Clinical description	Objective criteria
0	0	Asymptomatic - no hemodynamically significant occlusive disease	Normal treadmill or reactive hyperemia test
	1	Mild claudication	Completes treadmill exercise; AP after exercise > 50 mmHg but at least 20 mmHg lower than resting value
I	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise, and AP after exercise < 50 mmHg
II	4	Ischaemic rest pain	Resting AP < 40 mmHg, flat of barely pulsatile ankle or metatarsal PVR; TP < 30 mmHg
III	5	Minor tissue loss - nonhealing ulcer, focal gangrene with diffuse pedal ischaemia	Resting AP < 60 mmHg, ankle or metatarsal PVR flat or barely pulsatile; TP < 40 mmHg
	6	Major tissue loss - extending above TM level, functional foot no longer salvageable	Same as category 5

AP: ankle pressure, PVR: pulse volume recording, TM: transmetatarsal, TP: toe pressure. Adapted from: Rutherford et al. 1997.

Some 1–3% of all PAD patients develop CLTI, defined as rest pain or tissue loss caused by an insufficient arterial blood supply.[13] The prevalence of CLTI in western

populations is between 0.05 and 0.25%.[17] Notably, up to 50% of patients presenting with CLTI may have had no prior history of PAD.[18] Patients treated for CLTI have a 1-year mortality of roughly 25% and a major amputation rate of 30%.[15] Diabetics in particular, are at high risk for both gangrene and limb loss.[8] The effect of cigarette smoking cannot be emphasised enough, as there is evidence of a significant reduction in both mortality and the number of amputations associated with smoking cessation among CLTI patients.[19]

Treatment of PAD includes modifications to lifestyle and diet, smoking cessation and pharmacological intervention. As atherosclerosis in PAD is often generalised, the management of CV risk factors is of the utmost importance in preventing major adverse CV events (MACE), such as myocardial infarction (MI) and stroke. Treatment of hypertension and hyperglycaemia is essential, as is preventive statin and anti-platelet therapy. The majority of current recommendations do not recommend anti-platelet therapy for asymptomatic PAD patients. However, anti-platelet therapy has been deemed "reasonable", although it has not been explicitly recommended, by both the AHA and the ACC. [4,9–11] Individual risk-benefit profiling of PAD patients has been suggested.[20] Adherence to recommended cardioprotective medication protocols among PAD-patients appears to be poor as compared to patients with coronary artery disease (CAD).[21] There is also apparent room for improvement among physicians to recognise PAD as a high-risk disease and offer the best pharmacologic treatment available for these patients.[22]

Arterial imaging using doppler ultrasound (DUS), digital subtraction angiography (DSA), computed tomography angiography (CTA) or magnetic resonance angiography (MRA) is a prerequisite for planning revascularisations.[4,9–11] The role of revascularisation for IC, especially among smokers, is not without controversy, although quality-of-life driven invasive treatment for significant functional disability remains generally accepted.[23–25] It is worth noting, that while arterial reconstruction significantly reduces the risk of limb loss in patients with CLTI, it has a negligible effect on mortality.[26]

Although most PAD patients are asymptomatic, the disease does predispose them to MACE, limb loss and death. Some studies report an over three-fold relative risk (RR) of death for any reason over 10 years, and an almost six-fold RR of death from CV reasons, when compared to the general population.[27,28] Polyvascular disease is any combination of PAD, cerebrovascular disease and CAD that predisposes to MACE. It has been reported to be present in 16% of patients with any symptomatic arterial disease (Figure 1).[29] Similarly, increased crude rates of mortality and MACE have been found in patients with clinically established PAD and those with subclinical PAD, when compared to disease-free patients.[30] Moreover, even borderline PAD has been associated with an increased risk of functional decline.[31]

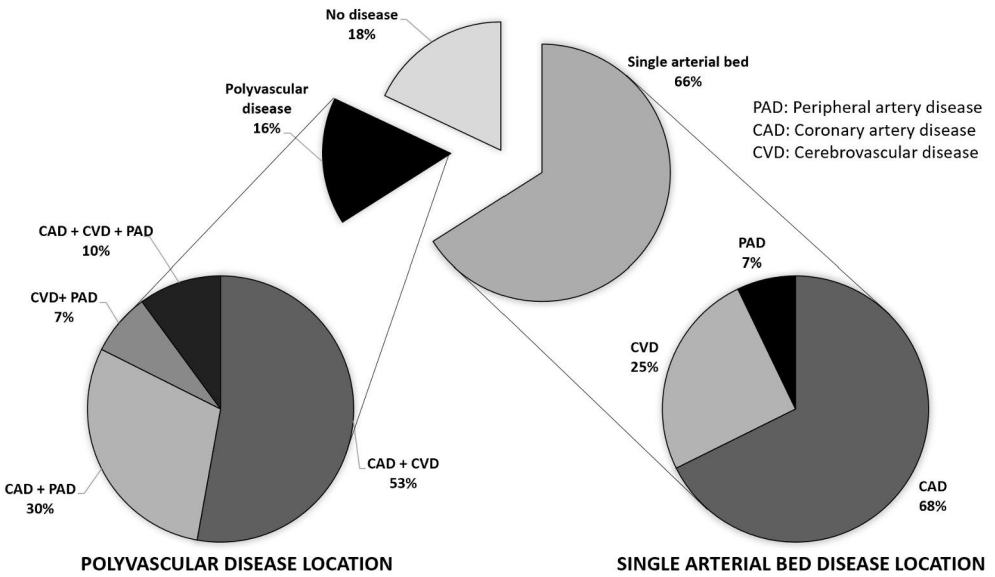


Figure 1. Prevalence and distribution of vascular disease in the REACH registry. Adapted from: Bhatt et al. 2016.

PAD imposes a substantial economic burden on society. In 2001 in the USA alone, the cost of treatment directly associated with PAD was estimated at 4.37 billion USD.[32] Roughly half of the cost of hospitalisations of PAD patients is accounted for by the treatment for lower limb symptoms, and half by the treatment for MACE.[33]

Conventional risk factor-based models may over- and underestimate CV risk, especially in individuals with extreme risk factors, and in those with pre-existing CV disease.[34] There is an apparent need for more accurate and incremental assessment of CV risk, particularly in the asymptomatic PAD population, where aggressive conservative therapy may have a marked influence on prognosis.[35] A significant proportion of patients that meet the CLTI criteria will undergo major amputation or die within a few years from diagnosis. Conversely, a significant percentage of these patients have been reported to survive without amputation, and even with no revascularisation.[36] Although extensive surgical revascularisation in octogenarians with CLTI yields patency and limb salvage similar to that in younger patients, perioperative mortality is ten-fold.[37] Better risk stratification among CLTI patients is therefore crucial, in order to direct more effectively resources and aggressive treatment to where the benefits will be the greatest. This thesis attempts to clarify the role of two commonly utilised investigative modalities: angiographic imaging and peripheral pressure measurements to assess risk in symptomatic PAD patients.

2 Review of the Literature

2.1 Prognosis in Peripheral Artery Disease

Keeping in mind that the prevalence of PAD increases with age, all-cause mortality in patients with PAD may be as high as 30% at 5 years, 50% at 10 years and 70% at 15 years after diagnosis.[38] It was reported that 40.7% of patients died within a median follow-up of 5.9 years in an unselected U.S. Veterans Health Administration population of 155647 predominantly (97.9%) males with an incident PAD diagnosis.[39] A British retrospective, observational cohort study compared CV outcome in 28484 symptomatic PAD patients with 113940 matched controls for a median follow-up time of 5.3 and up to 8 years. PAD patients had a significantly higher hazard, as measured by hazard ratio (HR), of all-cause death (HR 1.4 [95% confidence interval {CI} 1.38–1.43]), CV death (HR 2.1 [95% CI 1.9–2.2]), MI (HR 1.7 [95% CI 1.6–1.8]) and stroke (HR 1.5 [95% CI 1.4–1.6]), than the non-PAD controls.[40]

A widely cited prospective study by Criqui et al. followed 408 control subjects and 67 PAD patients with so-called isolated large-vessel disease for 10 years. Large-vessel disease was, as defined in that study by segmental pressure measurements and arterial flow velocities to be located above the ankle. Large-vessel PAD greatly increased the risk of all-cause mortality (RR 3.1 [95% CI 1.9–4.9]) and particularly death from MACE (RR 5.9 [95% CI 3.0–11.4]) and CAD (RR 6.6 [95% CI 2.9–14.9]), in comparison to controls. Differences in risks of patients with known, pre-existing CV disease and those without were small, suggesting that a substantial proportion of asymptomatic PAD patients without diagnosed coronary or cerebrovascular disease (CVD) had silent but significant atherosclerosis of those vascular beds as well. Risks were higher overall in men than in women, and higher with worsening clinical PAD symptoms.[28]

In the Edinburgh Artery Study (EAS), a prospective cohort study with 1592 subjects, RR of CV death at 5-year follow-up was higher for asymptomatic PAD patients than for controls, and highest in patients with IC. However, the same study found no difference in RR for overall mortality. Although the EAS primarily enrolled 1592 subjects, the number of patients with IC available for analysis was only 73, and RRs were adjusted for age only.[41] The get-ABI study, a German prospective

observational cohort study of individuals ≥ 65 years old, included 5392 control subjects, 836 individuals with asymptomatic PAD and 593 patients with symptomatic PAD. After 5-year follow-up, the respective adjusted HR for a composite endpoint of death, MACE or revascularisation was 1.8 (95% CI 1.5–2.1) for asymptomatic PAD and 2.7 (95% CI 2.3–3.2) for symptomatic PAD, when compared to non-PAD controls. No difference in risk for MI, stroke or amputation was found between PAD groups. In this study, patients with ABI > 1.5 were excluded.[42] Within a high-risk cohort of 1022 patients undergoing coronary artery bypass grafting, adjusted HRs for overall mortality in subjects with symptomatic and asymptomatic PAD versus PAD-free controls, were 2.6 (95% CI 1.6–4.5) and 2.2 (95% CI 1.3–3.7), respectively, and for CV mortality 3.4 (95% CI 1.7–6.7) and 3.3 (95% CI 1.7–6.6), respectively.[43]

Mortality of PAD is generally higher with clinically progressing degrees of ischaemia, as illustrated in two early patient series from 1977 and 1987. In the first study, 103 patients who underwent femoropopliteal bypass had 10-year mortalities of 48%, 80% and 95% when initially presenting with IC, rest pain and gangrene, respectively.[44] In the latter study, 932 patients who had received an infrainguinal bypass had 5-year cumulative mortality rates of 23%, 45% and 52% for IC, rest pain and necrosis, respectively.[45] A large Dutch national registry study compared outcomes for hospitalised and day-clinic patients against a general population sample. They obtained adjusted 5-year respective HRs for men and women with IC of 1.8 (95% CI 1.6–2.1) and 1.7 (95% CI 1.6–1.8) for all-cause mortality, and 2.3 (95% CI 2.1–2.6) and 2.4 (95% CI 2.1–2.6) for CV mortality. Corresponding HRs for men and women with CLTI were 3.0 (95% CI 2.8–3.3) and 2.2 (95% CI 2.1–2.4) for all-cause mortality and 4.0 (95% CI 3.5–4.5) and 2.7 (95% CI 2.5–3.1) for CV mortality.[46] A Swedish prospective population study with 5080 subjects and 10-year follow-up showed stratification of overall mortality and CV mortality according to PAD severity, although HRs were only adjusted for age. Compared to disease-free controls, the age-adjusted HRs for all-cause mortality for asymptomatic PAD patients, IC patients and patients with severe limb ischaemia, defined as lowest ankle pressure (AP) ≤ 70 mmHg, were 1.6 (95% CI 1.4–1.8), 2.0 (95% CI 1.7–2.3) and 2.3 (95% CI 1.8–3.1), respectively. Corresponding HRs for CV mortality were 1.9 (95% CI 1.5–2.3), 2.6 (95% CI 2.1–3.4) and 3.5 (95% CI 2.3–5.2), respectively.[47] Symptomatic PAD has been associated with a two-fold all-cause mortality (HR 1.9 [95% CI 1.3–2.0]) in coronary artery bypass graft (CABG) patients.[30] A Swedish retrospective registry study comprising 16889 revascularised PAD patients reported the yearly incidence of major amputation was 0.4% in 6272 IC patients, compared to 12% at 6 months and 2% yearly thereafter for 10617 patients with CLTI. Amputation-free survival (AFS) at 3 years was 87.1% for IC patients and 51.2% for CLTI patients.[48]

Overall, patients with PAD have an increased risk of death and the risk is higher with increasing clinical severity of the disease. The risk of amputation is considerably high in patients with CLTI.

2.2 Intermittent Claudication

Although IC is a typical symptom of PAD, patients with PAD typically do not have claudication. In fact, claudication may be present in less than 10% of PAD patients.[49] CV risk associated with IC is well illustrated in the Quebec Cardiovascular Study. In that study population of over 4000 men with no clinical CVD at baseline, adjusted risk of all-cause mortality was as high in patients with incident IC as it was in incident MI-survivors.[50] Reunanen et al. studied a cohort of 30–59-year-old Finnish men and women. Even adjusting for age in this relatively young group, IC increased the risk of all-cause and CV mortality in men but not in women. This independent association was lost after adjusting for symptoms and signs of CAD, which were highly prevalent in the study population.[51] In a subgroup analysis of IC patients in the Framingham study, 44% of men and 34% of women had coexisting CAD, and 43% and 49% of men and women, respectively, aged between 50 and 76 years, had MACE within 6 years of onset of IC. By 10 years, 24% of men and 41% of women aged 30 to 76 years, had died of CV conditions.[52] In the EAS, age-adjusted RR for CV death with IC compared to controls without PAD was 2.7 (95% CI 1.3–5.3), although for overall mortality the increase in risk was not significant.[41]

The Whitehall study recruited 18388 men aged 40–64 years, in the late 1960's. 147 subjects with probable IC (typical calf claudication) and 175 with possible IC (calf pain disappears while walking) were identified by a questionnaire. Within a follow-up period of 17 years, age adjusted all-cause mortality with possible and probable IC was approximately doubled, and mortality from CAD and cerebrovascular disease almost tripled from that of non-claudicating participants. After full adjustment, RRs of all-cause mortality were 1.9 (95% CI 1.5–2.4) and 1.7 (95% CI 1.3–2.3) for possible and probable IC, respectively. In comparison, the RRs for CV mortality were 2.1 (95% CI 1.5–2.8) for possible IC and 2.7 (95% CI 2.0–3.7) for probable IC.[53] An Israeli prospective cohort study of male government officials conducted between 1965 and 1986 included 360 men with IC and 7983 asymptomatic men and found a 50% increase in adjusted risk of all-cause mortality with IC (RR 1.5 [95% CI 1.3–1.8]). In this particular study, mortality was predominantly driven by stroke-related deaths (RR 2.8 [95% CI 1.9–4.0]), as adjusted CAD mortality or non-CV mortality did not significantly differ from subjects without IC.[54]

Traditionally, the risk of amputation in IC has been considered to be relatively low, even though 8-year amputation rates of up to 30% have been stated in early

studies.[55] The 1–3% 5-year risk stated in the Trans-Atlantic Inter-Society Consensus (TASC) II recommendation is often quoted, but most studies report significantly higher figures.[15] A review article authored in 1989 by McDaniel and Cronenwett summarises several historical studies with yearly amputation rates of approximately 1% in patients with claudication.[56] A significant proportion of patients with IC have peripheral pressures that meet CLTI criteria. Jelnes et al. reported that 17% of 257 consecutive IC patients had a toe pressure (TP) of < 30 mmHg and 6.8% were amputated within 5 years.[57] According to a contemporary meta-analysis, 21% of patients presenting with IC may develop CLTI over time, and as many as 4% to 21% will be amputated.[16] In the EAS, 1.4% of 73 subjects with IC in the cohort developed ulcers within 5 years, and 4.1% underwent amputation.[41] Dormandy and Murray reported 1-year outcomes in a subgroup of 1969 placebo-receiving patients with IC from a clinical trial. During 1-year, 4.3% died and 1.6% underwent major amputation.[58] In a contemporary setting of IC patients receiving in-hospital treatment, Hackl et al. prospectively followed 129 patients for an average of 8.8 years, during which 10% underwent amputation of the treated extremity.[59]

Patients with IC are a heterogenous group, with a possibly significant proportion having critically low TP, although not meeting clinical CLTI criteria as noted above. Their increased risk of death compared to asymptomatic individuals appears to be driven by CV mortality. The risk of progression to CLTI and amputation may be higher than generally acknowledged.

2.3 Chronic Limb-threatening Ischaemia

The prognosis for CLTI is bleak, even when accounting for the fact that CLTI patients tend to be relatively old and suffer from multiple comorbidities.[48] 1-year (20%), 2-year (40%), 5-year (40–70%) and 10-year (80–95%) mortality in CLTI patients is comparable to many a malignant disease.[60,61] In a meta-analysis of 13 studies with a total of 1527 conservatively treated CLTI patients, 1-year all-cause mortality was 22%.[62] This figure does not differ much from studies also involving revascularised patients, such as the Cohorte de Patients Artériopathes (COPART) registry study. In that study, 940 patients were hospitalised for PAD, the majority of whom (63.6%) had CLTI or non-embolic ALI, and the rest (27.4%) IC, and were observed for 1 year. Mortality was as follows: 28.7% in patients with tissue loss, 23.1% with rest pain, 23% with ALI. Meanwhile, 1-year mortality for IC was 5.7%.[63] In a subgroup analysis of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, 128 patients with ALI or CLTI had an 8.3% risk of death and 3.7% risk of MACE at 1 year.[64]

Reinecke et al. assessed the outcome for over 40000 PAD patients in a German registry study, with 5353 Rutherford class 4, 6916 Rutherford class 5 and 8416

Rutherford class 6 patients. Compared to non-CLTI patients, Rutherford class 4–6 showed stratification of both estimated rates (18.9% vs. 37.7%, 52.2% and 63.5%, respectively) and adjusted hazard (HR 2.0 [95% CI 1.9–2.2]; HR 2.5 [95% CI 2.4–2.7]; HR 3.8 [95% CI 3.6–4.0], respectively) for 4-year mortality.[65] A similar stratification of mortality by Rutherford class was observed by Soga et al. in 995 endovascularly treated CLTI patients, with increasing adjusted odds ratios (OR) for 2-year mortality. The OR for Rutherford class 5 was 1.9 (95% CI 1.3–2.7) and for Rutherford class 6, 3.4 (95% CI 2.2–5.2), When compared to Rutherford class 4 patients.[61]

A registry study with almost 17000 patients by Baubeta Fridh et al. found that even though surgical or endovascular revascularisation significantly improved limb salvage in patients with CLTI, 3-year AFS remained low at 49% even in the revascularised patients for whom MACE accounted for the majority of deaths.[48] Abu Dabrh et al. reported a 1-year major amputation rate of 22% in their meta-analysis of conservatively treated CLTI patients.[62] 1-year amputation rates in the COPART study were 27.5% for CLTI with tissue loss, 12.6% for CLTI with rest pain, 12.6% for non-embolic ALI and 0% for IC.[66] In a subsequent subgroup analysis of the same cohort, amputation in patients with CLTI occurred in 23% within one year. The rate was 27% in conservatively treated patients and 17% in surgically revascularised patients. 1-year AFS was 55% and survival without amputation or MACE only 37%.[63] In the COMPASS trial, the subgroup of 128 patients with ALI or CLTI had a 20.5% 1-year risk of major amputation.[64] 4-year amputation rates in the registry study by Reinecke et al. for non-CLTI versus Rutherford class 4, 5 and 6 CLTI patients were 4.6%, 12.1%, 35.3% and 67.3%, respectively. Adjusted HRs for Rutherford classification 4, 5 and 6 CLTI patients, compared to non-CLTI patients were 3.1 (95% CI 2.8–3.5), 9.3 (95% CI 8.5–10.2) and 29.0, (95% CI 26.7–31.6), respectively.[65]

A recent meta-analysis of 124 randomised controlled trials and observational studies compared outcomes in CLTI patients against patients with non-critical PAD. The RRs for all-cause mortality (2.3 [95% CI 1.8–2.9]) and major amputation (3.9 [95% CI 2.5–5.9]) were clearly higher for CLTI, but the RR for CV mortality was only marginally increased (1.42 [95% CI 1.01–2.01]).[67]

Overall prognosis in CLTI is remarkably poor with a high short to medium term risk for both amputation and death. Even within this well-defined group, risk seems to increase in association with increasing clinical stages of critical ischaemia.

2.4 Lesion Distribution

Arterial imaging to assess the severity and distribution of atherosclerotic lesions is a prerequisite for invasive vascular surgery and endovascular therapy in patients with PAD. Some form of imaging is undertaken for most patients being considered for

revascularisation. Although some vascular specialists still consider conventional angiography the gold standard in arterial imaging, CT- and magnetic resonance angiography (MRA) allow rapid, non-invasive imaging of very large segments of arteries, which provides large amounts of quantifiable data.

2.4.1 Angiographic Classification Systems

Anatomical angiographic classification systems have been developed in order to design, measure and compare effectiveness of clinical trials and treatment protocols for PAD. In 1975, Vogelberg et al. were the first to grade the severity and distribution of angiographically detected atherosclerotic lesions in their study of patients with IC according to the following: predominant type of hyperlipoproteinaemia, diabetes and smoking status. A sclerosis index was calculated, ranging from 1–9 per pelvic, thigh and distal artery segment, giving a total score of 0–27 for each leg, or 0–54 for both legs (Table 3).[68] Later, a modified sclerosis index was used, where proximal and distal crural segments were assessed separately.[69] The Bollinger classification used in the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial, further divided the vascular bed into 10 segments. The Bollinger score is calculated according to the extent and severity of stenoses in each artery, while taking changes in lesion status into account (Table 4).[70,71] Graziani's morphological classification of disease severity purported to be useful for diabetics specifically, as it laid the emphasis on distal vasculature and the initial study only included diabetics with tissue loss (Table 5). Graziani's classification is inversely associated with transcutaneous oxygen pressure ($TcPO_2$),[72] but has not been shown to be associated with patient outcome.[73]

Table 3. Sclerosis index.

Number of lesions per segment	Degree of stenosis (%)	Sclerosis index
≤ 3	< 50	1
	> 50	2
	100	3
> 3	< 50	2
	> 50	4
	100	6
Ubiquitous	< 50	3
	> 50	6
	100	9

Index for pelvic + thigh + distal arteries gives a score of 0–27 for each leg. Adapted from: Vogelberg et al. 1975.

Table 4. Bollinger classification.

Lesion type	Degree of stenosis (%)	Score
Single	< 25	1
	25 - 50	2
	> 50	3
	Total occlusion	13
Multiple, ≤ 50 % of segment	< 25	2
	25 - 50	3
	> 50	5
	Total occlusion	13
Multiple, > 50 % of segment	< 25	3
	25 - 50	4
	> 50	6
	Total occlusion	16
Follow-up:	≥ 2 cm decrease	-1
	≥ 2 cm increase	1

Score calculated separately for: abdominal aorta; common, external and internal iliac; superficial and deep femoral; popliteal; anterior, posterior tibial, and fibular arteries. Adapted from: Bollinger et al. 1981.

Table 5. Graziani's morphologic classification of disease severity.

Class	Angiographic finding
1	Isolated, one vessel tibial or peroneal artery obstruction
2a	Isolated femoral/popliteal artery or two below knee arteries obstructed but with patency of one of the two tibial arteries
2b	Isolated femoral/popliteal artery or two below knee tibial arteries obstructed but with patency of the peroneal artery
3	Isolated, one artery occluded and multiple stenoses of tibial/peroneal and/or femoral/popliteal arteries
4	Two arteries occluded and multiple stenoses of tibial/peroneal and/or femoral/popliteal arteries
5	Occlusion of all tibial and peroneal arteries (below knee cross-sectional occlusion)
6	Three arteries occluded and multiple stenoses of tibial/peroneal and/or femoral/popliteal arteries
7	Multiple femoropopliteal obstructions with no visible below the knee arterial segments

Adapted from: Graziani et al. 2007.

The TASC I and TASC II undertook the effort of providing the anatomic classification of PAD. Initially, aortoiliac and femoropopliteal segments were grouped according to lesion patterns into A-D categories by increasing complexity, with the intent of providing recommendations for choosing surgical or endovascular treatment modality (Figure 2 and 3, table 6 and 7).[15,38] The recommendation was later modified to include below-the-knee arteries (Figure 4, table 8).[74] Although the lesion-based approach in the original TASC II classification may be considered obsolete due to unforeseen and rapid advancements in endovascular therapy, the classification remains widely used as a descriptive tool within vascular research.

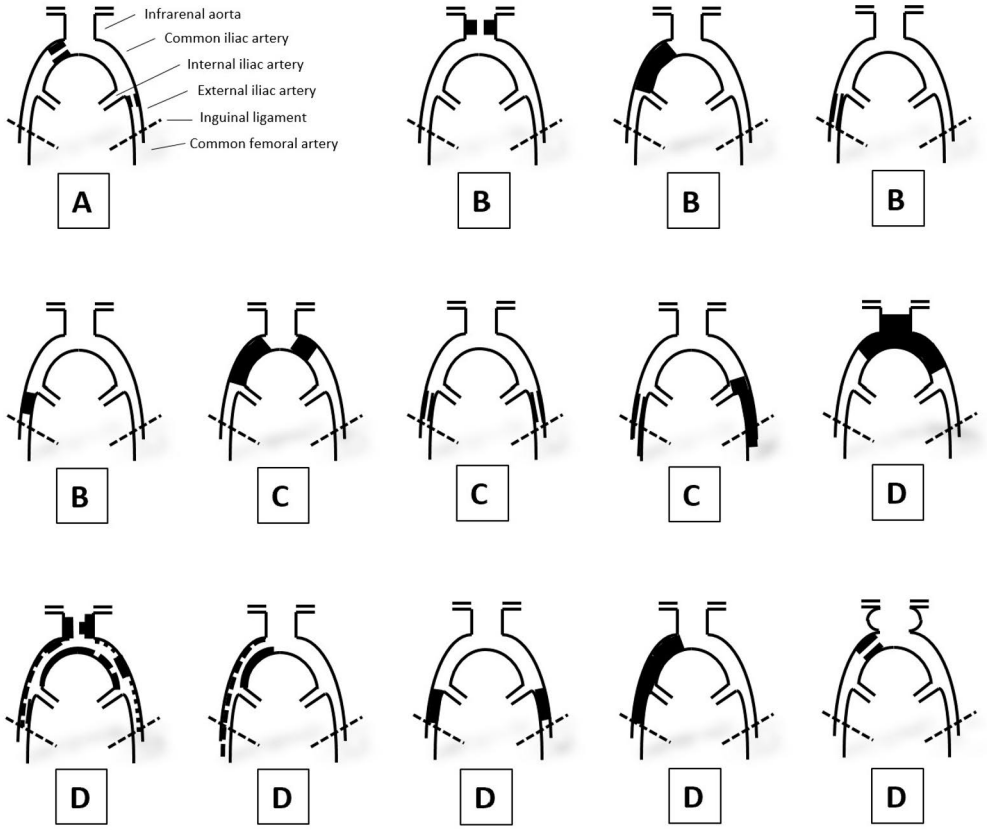


Figure 2. TASC II classification of aortoiliac lesions; examples. Adapted from: Norgren et al. 2007.

Table 6. TASC II classification of aortoiliac lesions.

TASC class	Lesion type
A	• Uni- or bilateral CIA stenosis • Uni- or bilateral single ≤ 3 cm EIA stenosis
B	• ≤ 3 cm stenosis of infrarenal aorta • Unilateral CIA occlusion • Single or multiple stenosis totaling 3-10 cm involving EIA not extending into CFA • Unilateral EIA occlusion not involving IIA origin or CFA
C	• Bilateral CIA occlusion • Bilateral EIA stenoses 3-10 cm long not extending into CFA • Unilateral EIA stenosis extending into CFA • Unilateral EIA occlusion involving origins of IIA and/or CFA • Heavily calcified unilateral EIA occlusion with or without involvement of the origins of IIA and/or CFA
D	• Infrarenal aortoiliac occlusion • Diffuse disease involving aorta and both iliac arteries • Diffuse multiple stenoses involving unilateral CIA, EIA and CFA • Unilateral occlusion of CIA and EIA • Bilateral EIA occlusions • Iliac stenoses in patients with AAA not amenable to endograft placement

CIA: common iliac artery; EIA: external iliac artery; CFA: common femoral artery; IIA: internal iliac artery; AAA: abdominal aortic aneurysm. Adapted from: Norgren et al. 2007.

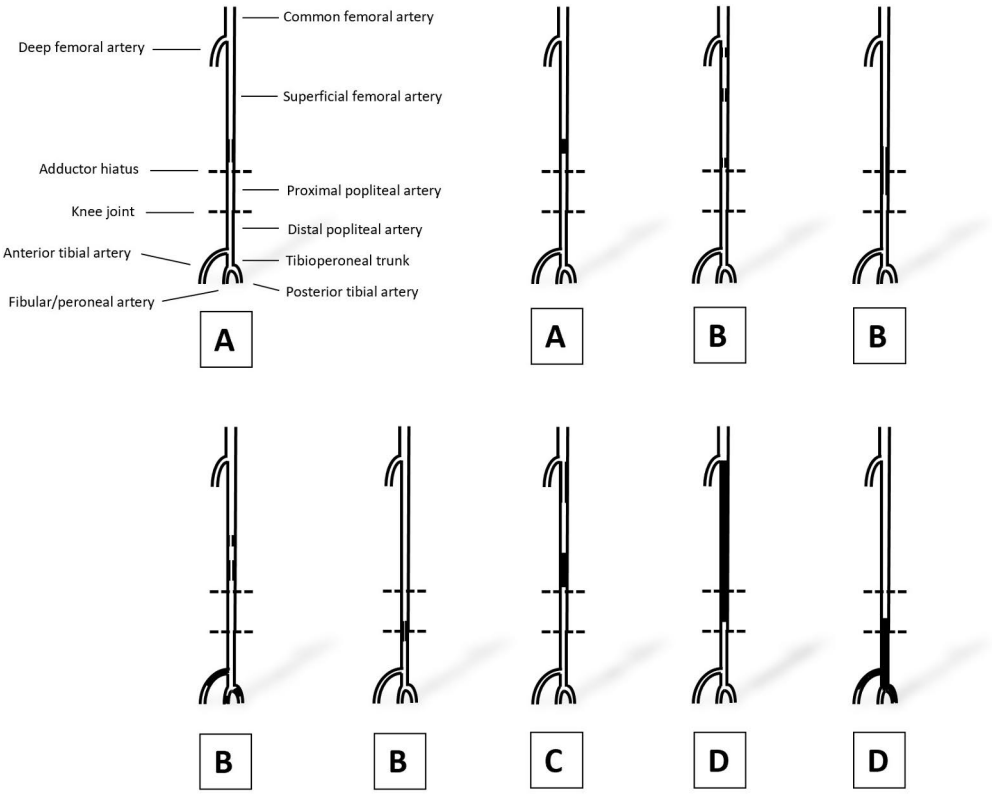


Figure 3. TASC II classification of femoropopliteal lesions; examples. Adapted from: Norgren et al. 2007.

Table 7. TASC II classification of femoropopliteal lesions.

TASC class	Lesion type
A	• Single stenosis ≤ 10 cm • Single occlusion ≤ 5 cm
B	• Multiple stenoses or occlusions, each ≤ 5 cm • Single stenosis or occlusion ≤ 15 cm not involving distal PA • Heavily calcified occluson ≤ 5 cm • Single PA stenosis
C	• Multiple stenoses or occlusions totaling > 15 cm with or without heavy calcification • Recurrent stenoses or occlusions after failing treatment
D	• CTO of CFA or SFA (> 20 cm), involving PA • CTO of PA and proximal trifurcation vessels

PA: popliteal artery; CTO: chronic total occlusion; CFA: common femoral artery; SFA: superficial femoral artery. Adapted from: Norgren et al. 2007.

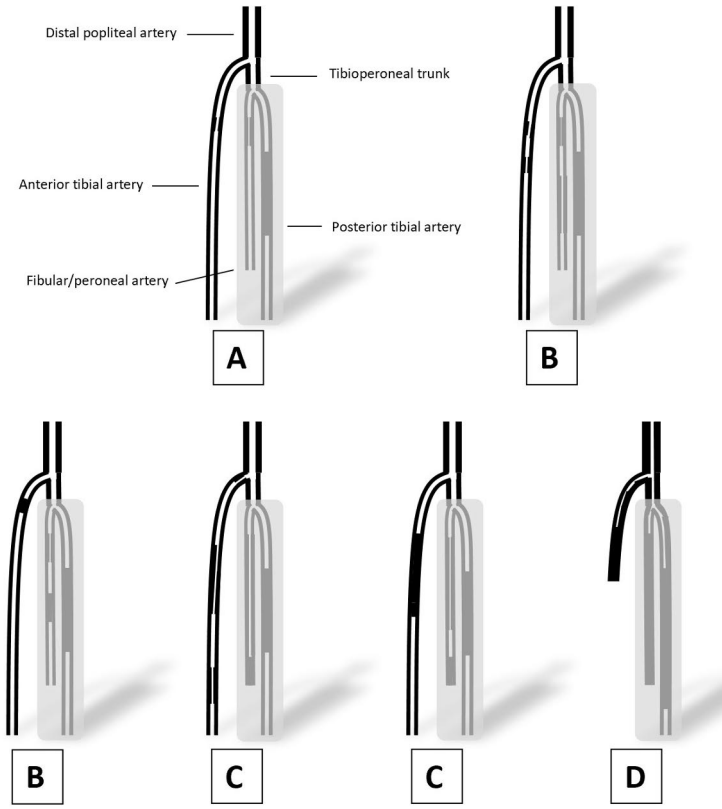


Figure 4. TASC II classification of infrapopliteal lesions; examples with anterior tibial artery as target vessel. Adapted from: Jaff et al. 2015.

Table 8. TASC II classification of infrapopliteal lesions.

TASC class	Lesion type
A	• Single focal stenosis ≤ 5 cm in the target artery, with occlusion or stenosis of similar or worse severity in the other tibial arteries.
B	• Multiple stenoses, each ≤ 5 cm, or total length ≤ 10 cm, or single occlusion ≤ 3 cm in target artery, with occlusion or stenosis of similar or worse severity in other arteries.
C	• Multiple stenoses in target artery and/or single occlusion with total lesion length > 10 cm, with occlusion or stenosis of similar or worse severity in other arteries.
D	• Multiple occlusions involving target artery with total lesion length > 10 cm or dense lesion calcification or non-visualization of collaterals. Other arteries occluded or densely calcified.

Adapted from: Jaff et al. 2015.

The Global Limb Anatomic Staging System (GLASS) for CLTI represents a more contemporary definition of anatomic classification of lesion severity, with an evident emphasis on endovascular revascularisation. With the presumption of no significant aortoiliac or common femoral artery stenoses, femoropopliteal and crural artery lesions along an intended target arterial path of revascularisation to the foot are graded 0–4 according to lesion length, severity and location (Figure 5 and 6, Table 9 and 10). Cross-tabulation of these gives a stage ranging from I to III (Table 11). Increasing GLASS stages purportedly correlate with an increasing risk of technical failure and lower limb-based patency, i.e., preservation of inline flow through the target arterial path. The GLASS system does not take into account the patency of the deep femoral artery. Although an inframalleolar/pedal descriptor that ranges from 0–3 and depicts pedal outflow is determined, it has not been incorporated into GLASS staging.[14]

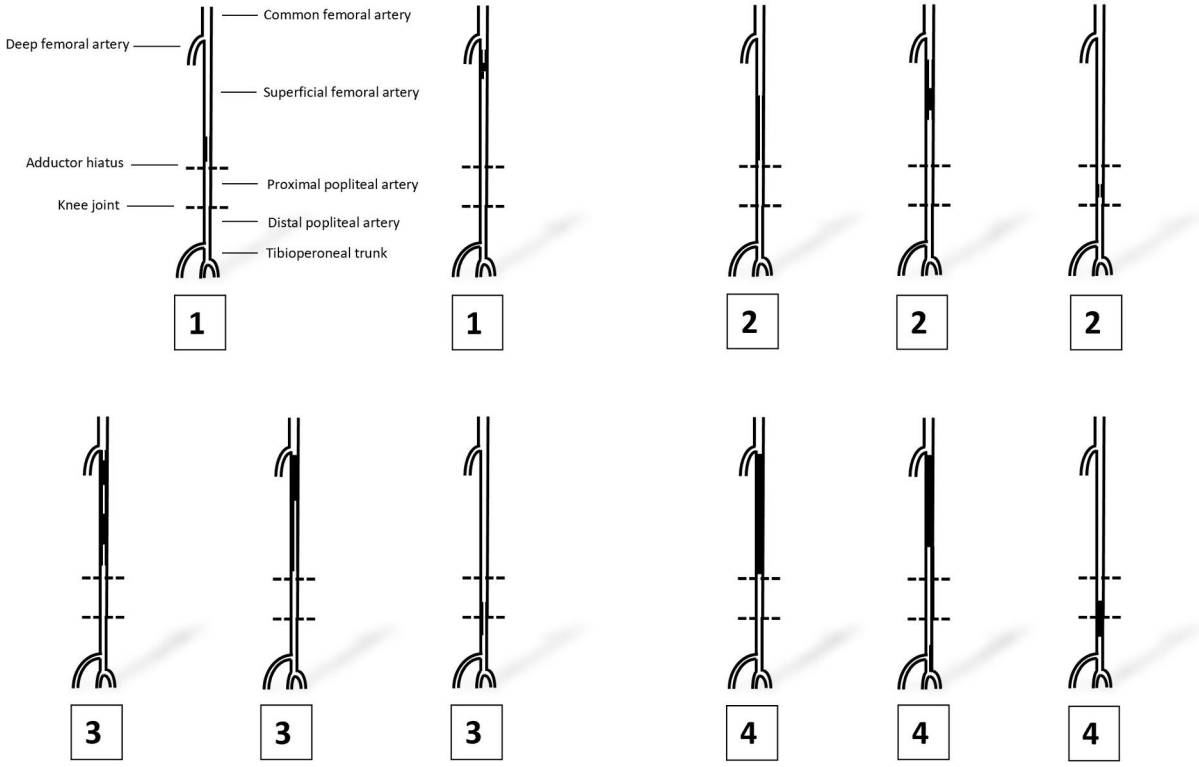


Figure 5. GLASS; grading of femoropopliteal lesions; examples. Adapted from: Conte et al. 2019.

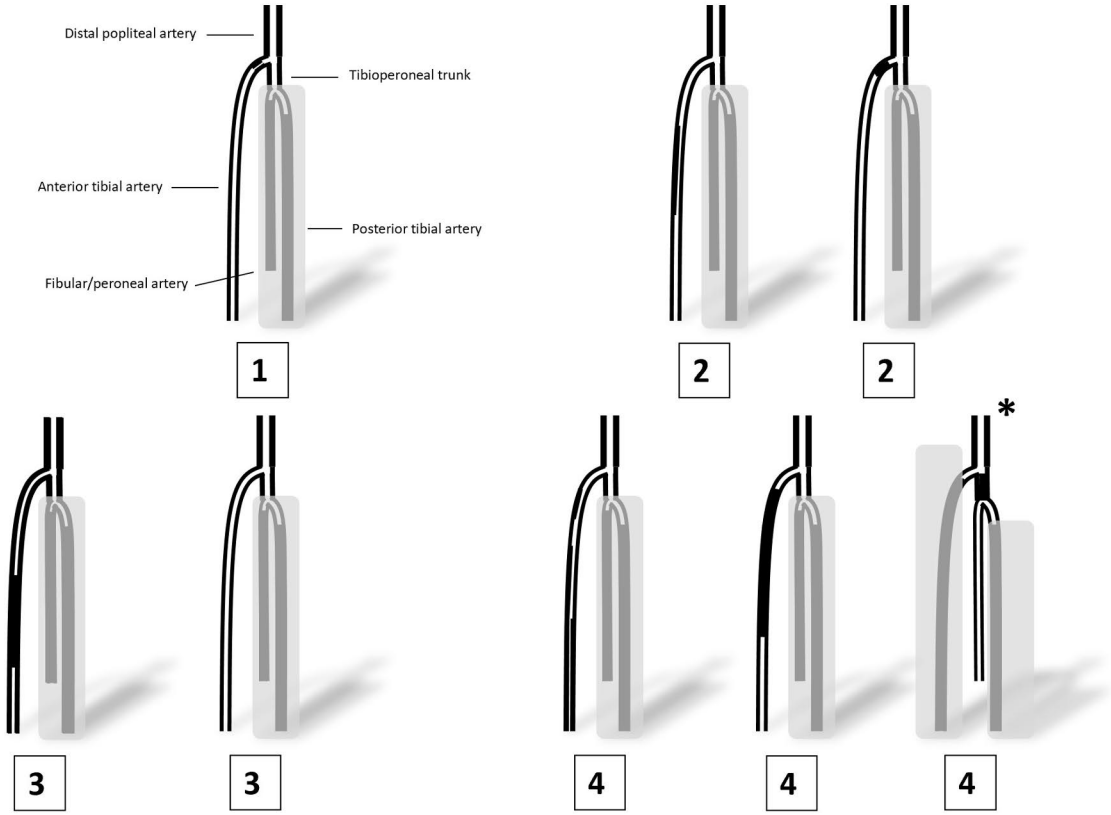


Figure 6. GLASS; grading of infrapopliteal lesions; examples with anterior tibial artery as target arterial path (peroneal in *). Adapted from: Conte et al. 2019.

Table 9. Global Limb Anatomic Staging System (GLASS); Grading of femoropopliteal disease.

Grade	Description
0	• No significant (< 50%) disease
1	• Total length SFA disease < 1/3 (< 10 cm) • May include single focal CTO (< 5 cm) as long as not flush occlusion • Popliteal artery with mild or no significant disease
2	• Total length SFA disease 1/3 - 2/3 (10-20 cm) • May include CTO totaling < 1/3 (< 10 cm) but not flush occlusion • Focal popliteal artery stenosis < 2 cm not involving trifurcation
3	• Total length SFA disease > 2/3 (> 20 cm) in length • May include any flush occlusion < 20 cm or non-flush CTO 10-20 cm long • Short popliteal stenosis not involving trifurcation
4	• Total length SFA occlusion > 20 cm • Popliteal disease > 5 cm or extending into trifurcation • Any popliteal CTO

SFA: superficial femoral artery; CTO: chronic total occlusion. Adapted from: Conte et al 2019.

Table 10. Global Limb Anatomic Staging System (GLASS); Grading of infrapopliteal disease.

Grade	Description
0	• No significant (< 50%) disease in target arterial path
1	• Focal stenosis of tibial artery < 3 cm
2	• Stenosis involving 1/3 total vessel length • May include focal CTO (< 3 cm) • Not including TP trunk or tibial vessel origin
3	• Disease up to 2/3 vessel length • CTO up to 1/3 length (may include tibial vessel origin but not TP trunk)
4	• Diffuse stenosis > 2/3 total vessel length • CTO > 1/3 vessel length (may include vessel origin) • Any CTO of TP trunk if ATA is not the target artery

CTO: chronic total occlusion; TP: tibioperoneal; ATA: anterior tibial artery. Adapted from: Conte et al 2019.

Table 11. Assignment of Global Limb Anatomic Staging System (GLASS) stage.

		IP grade				
		0	1	2	3	4
FP grade	0	(n/a)	I	I	II	III
	1	I	I	II	II	III
	2	I	II	II	II	III
	3	II	II	II	III	III
	4	III	III	III	III	III

FP: femoropopliteal; IP: infrapopliteal. Adapted from: Conte et al. 2019.

2.4.2 Risk Factors and Lesion Distribution

Smoking, male sex and relatively younger age have been related to atherosclerotic aortoiliac lesions.[75–78] Smoking has also been associated with atherosclerotic lesions at the femoropopliteal level.[73,75,79] It is commonly accepted that PAD lesions are frequently infragenicular in diabetic patients,[75,76,78–83] but even extensive disease of the profunda femoris has been associated with diabetes,[83,84], and increasing age with infragenicular lesions.[78] Hypertension has been associated with aortoiliac and femoropopliteal,[75] and distal lesions.[76] (Figure 7)

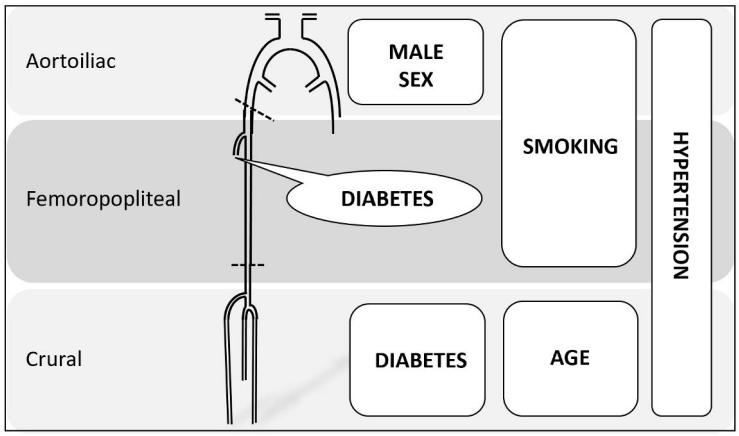


Figure 7. Risk factors and lesion distribution. Wickström 2022.

2.4.3 Whole-Body and Major Arteries

A total atherosclerotic score or atherosclerosis index calculated from whole-body MRA by assessing several arterial segments, correlates closely with risk factors compiled into the Framingham risk score.[85,86] In a meta-analysis of 30 prospective studies, with mortality data reported for over 40000 subjects, calcification at any site (mitral valve, aorta, coronary, carotid, iliac, femoral, or breast artery), increases the odds of coronary events (OR 3.7 [95% CI 2.6–5.5]), stroke (OR 2.2 [95% CI 1.8–2.7]) and death (OR 3.9 [95% CI 2.4–6.5]).[87] Allison et al. reviewed CT scans obtained from 4544 patients to measure calcification within different vascular locations, namely the coronary arteries, abdominal aorta, iliac arteries, thoracic aorta and carotid arteries. After full adjustment, the HR for overall mortality was increased with calcifications in the carotid arteries (HR 1.60 [95% CI 1.03–2.49]) and thoracic aorta (HR 2.1 [95% CI 1.2–3.5]). In survival analysis, calcification of the carotid arteries, thoracic aorta and iliac arteries denoted the lowest probability of survival. No significant differences in freedom from cardiovascular death (FCD) was observed between the groups.[88] All-cause and CV mortality in diabetic patients have been associated with a multi-bed vascular calcification score, derived from CT of the coronary and carotid arteries and the abdominal aorta. After adjusting for the usual risk factors and for the Framingham risk score, both associations were linear, with each standard deviation (SD) increase of the score, which increased the HR of all-cause mortality by 1.5 (95% CI 1.3–1.8) and CV mortality by 1.7 (95% CI 1.3–2.1).[89]

There are several studies of coronary artery calcification and CV risk. The degree of coronary artery calcification (CAC) was independently associated with both CAD- and overall mortality, and added incremental prognostic accuracy in combination with traditional risk factors.[90–93] Although thoracic aortic calcium

(TAC) did not seem to improve the predictive ability of CAC for coronary events,[94] TAC has been associated with stroke, aortic aneurysm and PAD.[95] A study of 958 asymptomatic heavy smokers showed that, after adjusting for CAC among other risk factors, the presence of TAC was associated with increased all-cause mortality (HR 1.6 [95% CI 1.1–2.3]).[96] However, in another prospective study of 3415 asymptomatic subjects with no CAC, TAC was crudely associated with mortality, but no significant association remained after adjusting for CVD risk factors.[97] Aortic arch calcification independently increased the RR of overall mortality by 1.3 (95% CI 1.1–1.7) and CV mortality by 1.8 (95% CI 1.1–2.7) per 1 SD increase, in a subgroup of the population-based Rotterdam Study with 2408 participants. Although increased calcification in any of the vascular beds studied was associated with increased overall and CV mortality after adjusting for age and sex, the association was greater for aortic arch calcification and CV mortality, than for the coronary, internal or external carotid arteries, and after adjusting for calcification in other vascular beds, only aortic arch calcification remained significantly associated with outcome.[98]

A part of the Framingham study, in which 2505 individuals were observed for over 20 years, showed that the degree of abdominal aortic calcification assessed from lateral lumbar radiographs was associated with incident CAD, CVD and CV mortality. Multivariable analysis by abdominal aortic calcium score tertiles effectively stratified the risks for all end points. The RRs for CV mortality in tertiles 2 and 3, compared to tertile 1, were 1.8 (95% CI 1.3–2.4) and 2.3 (95% CI 1.7–3.1), respectively. The risks were more pronounced in women.[99] A similar result was obtained in a meta-analysis of 3 studies with 4986 individuals, including the Framingham study, whereby abdominal aortic calcification was independently associated with CV mortality (RR 1.72 [95% CI: 1.03–2.86]).[35]

Calcification, as detected by varying imaging modalities, is an indicator of atherosclerosis. Increased calcification in major arteries, especially in the aorta, is associated with increased all-cause mortality, and CV mortality in particular.

2.4.4 Lower Extremity Arteries

Jonason et al. observed that mortality at 6 years, which was mainly cardiovascular, in 224 IC patients was higher with multiple stenoses (45%) when compared to a single stenosis (33%). A significantly greater proportion of patients with multiple stenoses had bilateral disease, and the difference in mortality resulted mainly from CAD, even though clinical baseline CAD characteristics between groups were similar.[100]

Jones et al. retrospectively calculated an Anatomic Runoff Score (ARS) that encompassed the following: bilateral stenoses and occlusions in the iliac to the

popliteal arteries, patency of the profunda femoris and number of crural runoff vessels. This calculation gave a score range of 0–15. After evaluating bilateral DSAs of 908 revascularised patients at a median of 3.4 years follow-up, the authors found that ARS ≥ 5 were independently associated with a two-fold risk of a composite end point of death or MACE (MI or stroke) in survival analysis. Every 2-point increase in ARS increased the HR by 1.2 (95% CI 1.1–1.4). All-cause mortality with ARS ≥ 5 was 29.3%, compared to 14.1% with ARS < 5. Survival analysis also showed a significant disadvantage in AFS for patients with ARS ≥ 5, compared to ARS < 5, with any amputation occurring in 17.7% and 6.6%, and AFS being 61.8% and 81.7%, respectively.[101]

Smolderen et al. studied 756 newly diagnosed PAD patients by quantifying the extent of lower extremity PAD using duplex doppler ultrasound (DDUS) and the simple determination of the number of lesions (1, 2 and ≥ 3). The authors disregarded stenosis degree, complexity and length in their evaluation. After a median follow-up of 3.2 years, ≥ 3 lesions increased the risk of MACE (HR 1.6 [95% CI 1.1–2.4]) and recurrent MACE (HR 1.5 [95% CI 1.1–2.2]), compared to only 1–2 lesions. All-cause mortality was 2.5-fold (95% CI 1.5–4.1) with ≥ 3 lesions.[102] Chowdhury et al. calculated Bollinger and lower limb arterial calcification (LLAC) scores of both lower extremities in 220 CT studies of symptomatic PAD patients. A good correlation between Bollinger score and LLAC was shown. All deaths within a median of 46 months follow-up occurred in the highest LLAC quartile. Although the crude association of both high Bollinger score and LLAC with mortality was evident, no multivariable analysis was done in their study.[103]

There are three frequently quoted papers on peripheral atherosclerotic lesion distribution that associate increased mortality with proximal disease localisation. Two of these studies rely on segmental pressure measurements, whereas the third utilises DSA. In 1985, Criqui et al. prospectively followed 567 subjects and compared all-cause mortality during a mean follow-up time of 4 years among patients with large-vessel PAD (LV-PAD) and isolated small-vessel PAD (SV-PAD). SV-PAD was defined by these authors as TBI < 0.7 with a normal ABI and below-knee brachial index or a combination of abnormal pulse reappearance half-time and post-occlusive reactive hyperaemia. The authors found that 69 patients had LV-PAD and 90 had isolated SV-PAD, which essentially affected the arteries below ankle level. Mortality in disease-free controls, LV-PAD patients and SV-PAD patients was 2.7%, 20.3% and 5.6%, respectively. Most deaths were due to cardiovascular causes in both LV- and SV-PAD patients. With LV-PAD, the adjusted RR for mortality was 4.2 (95% CI 1.8–10.0). Although crude mortality within the whole study population was twice as high for men than for women, LV-PAD associated mortality was higher in women. SV-PAD was not associated with mortality when subjected to multivariable analysis.[104] Vogt et al. classified 1162

patients according to multilevel, multisegmental or isolated aortoiliac, femoropopliteal and tibial disease, which were defined by segmental pressure measurements. They found 575 patients had unisegmental, 587 had multisegmental and 243 had no apparent disease. Patients with isolated tibioperoneal disease had the lowest adjusted RR of mortality in this study, not significantly different from disease-free controls. For men, the RR of all-cause mortality in order of increasing risk was 2.0 (95% CI 1.1–3.5) for isolated aortoiliac disease, 2.6 (95% CI 1.5–4.5) for isolated femoropopliteal disease, 3.5 (95% CI 2.0–6.1) for aortoiliac-femoropopliteal disease and 7.2 (95% CI 2.2–23.1) for disease in all three levels. The RR for women was 2.8 (95% CI 1.2–6.7) for isolated aortoiliac disease, 4.5 (95% CI 1.6–12.8) for aortoiliac-tibioperoneal disease and 5.3 (95% CI 2.3–12.2) for aortoiliac-femoropopliteal disease. The authors conceded, that due to the use of segmental pressure measurements, the study design had an inherent inability to detect tibioperoneal disease that did not involve all crural arteries.[75] Aboyans et al. retrospectively reviewed 400 symptomatic PAD patients undergoing their first DSA after a mean of 34 months follow-up. Patients were categorised by disease location into aortoiliac, femoropopliteal and infragenicular groups. No difference in mortality was found between the latter groups. In comparison to the infragenicular group, patients with proximal disease had a significantly higher mortality (HR 3.2 [95% CI 1.6–6.5]), and incidence of MACE or coronary or carotid revascularisation.[76]

Tern et al. conducted a retrospective study of infrainguinal Bollinger scores of 11 arterial segments, which were assessed by DUS in 678 patients with a median follow-up of 69 months. These authors showed that total Bollinger score was an independent predictor of mortality (OR 1.1 per 10 points [95% CI 1.1–1.2]). These authors further showed that femoropopliteal (OR 1.3 per 10 points) and crural Bollinger scores (OR 1.1 per 10 points [95% CI 1.1–1.2]) independently predicted mortality. The 95% CI for the OR of femoropopliteal Bollinger scores was erroneously reported as 1.11–1.08.[105] Chen et al. compared survival in 12731 referral outpatients by the absence or presence of PAD and the location of infrainguinal disease as determined by DUS thus: abnormal waveforms at the level of the common femoral artery were defined as proximal disease, and at foot and ankle level as distal disease. Compared with healthy subjects, adjusted mortality HRs were 1.3 (95% CI 1.3–1.4) for proximal and 1.5 (95% CI 1.4–1.6) for distal disease. After adjusting for ABI, only distal disease independently increased the hazard for mortality (HR 1.2, 95% CI 1.1–1.3).[79]

Existing evidence regarding the relationship between lesion location within lower extremity arteries, and mortality is controversial, which may partly be explained by heterogeneity in both methodology and the definitions used, especially in some of the older studies. Previous studies do, however, show general agreement

that more widespread atherosclerotic lesions predispose patients to increased mortality.

2.4.5 Crural Arteries

Whereas aortoiliac lesions tend to be associated with IC, crural disease is often associated with CLTI.[76,106] Disease progression in the crural arteries has been associated with diabetes.[107] Graziani et al. found 74% of lesions in diabetics with CLTI and foot ulcers (n=417) to be infragenicular.[72]

A prospective study authored by Stewart et al. was primarily designed to predict graft patency in 258 patients. In that study, run-off scores were calculated from handheld doppler signals obtained from the posterior, anterior tibial and dorsal pedal arteries prior to revascularisation. These scores were found to be associated with short-term mortality. Within 6 months, 50% of patients with a run-off score of 0, and 5% of patients with a run-off score of 4 were dead.[108] In a prospective 5-year evaluation of 226 revascularised patients, predominantly crural disease was independently predictive of ischaemic, haemorrhagic or embolic cerebrovascular events (HR 2.0 [95% CI 1.2–3.3]), compared to predominantly femoropopliteal disease. Estimated overall mortality was higher with predominantly crural disease, with a HR of 2.1 (95% CI 1.1–3.3).[109] In an analysis of the 452-patient BASIL cohort, an angiographic pre-intervention Bollinger score of below-the-knee arteries independently predicted 2-year mortality in CLTI patients with HRs of 2.0 (95% CI 1.2–3.2) for scores between 5–8 and 1.7 (95% CI 1.01–2.85) for scores ≥ 8, when compared to scores < 5. Neither TASC II classification, nor above-the-knee Bollinger score were independently associated with mortality.[110]

Isolated tibial disease was not an independent predictor of mortality or AFS, in a study of 446 revascularised CLTI patients by Gray et al. Although crude 3-year survival (50.4% vs. 62.6%) and AFS (35.1% vs. 50.2%) were lower in patients with isolated tibial disease versus patients with multi-level femoropopliteal disease with or without tibial disease, it was not independently associated with outcome.[73] Soga et al. were also unable to find an association between isolated infrapopliteal disease and mortality in 995 CLTI patients whom had undergone endovascular revascularisation.[61] Matsukura et al. calculated a modified Bollinger score at the ankle level including the pedal arch, in 104 patients and 118 limbs that had undergone crural bypass surgery. Although a score of > 45 significantly increased overall mortality and decreased AFS in patients with diabetes or end-stage renal disease (ESRD) in survival analysis, the increases were not significant in the overall study population.[111]

In 1975, Imparato et al. reported that the risk of amputation at a median of 2.5 years follow-up in 104 IC patients was associated with infrapopliteal arterial runoff.

Thus 12% of those patients with no runoff, 7% of those with 1–2 vessel runoff and 2% of those with 2–3 vessel runoff were amputated. No association with more proximal angiographic occlusions was found.[112] Faglia et al. calculated angiographic scores in 104 diabetic patients with foot ulcers by scoring the angiographic degree of stenoses from 0 to 3 in seven arterial segments from the iliac arteries to the crural arteries. The score was associated with amputation, which occurred in all patients with a score of > 14 and in no patients with a score < 10. Notably, the number of occluded popliteal and infrapopliteal arteries was primarily indicative of the risk of amputation with: 83.3–100% amputation rates in patients with 3–4 occluded arteries, a 54.5% amputation rate in those with 2 occluded arteries and an amputation rate of 3.6% in those with only one occluded artery.[81] Guzman et al. compared CT-derived Agatston calcium scores of the infragenicular arteries in 118 symptomatc PAD patients and 111 controls. The tibial calcification score increased significantly from controls to patients with IC and those with CLTI. After adjusting for risk factors, an increasing score was associated with worsening ischaemia. Receiver operating characteristic (ROC) analysis showed that the predictive value of the tibial calcification score was better than that of ABI for major and any amputation. The authors identified a cutoff value of 400 with a positive predictive value of 23% and a negative predictive value of 98% for major amputation. Multivariable analysis found that a score > 400 gave a HR of 11.3 (95% CI 1.4–93.8) for major amputation.[113]

The association of distally located PAD with amputations has previously been explained by the relative difficulty of performing distal revascularisations.[114,115] Fernandez et al. confirmed that patients with isolated tibial disease often have poor pedal runoff, lack of target vessels for revascularisation and often have systemic comorbidities that preclude surgical bypass, more often than do patients with multilevel disease. Crude estimated one-year limb salvage rates in initially endovascularly treated CLTI patients (123 patients and 136 limbs) were 74.8% for isolated tibial disease and 87.8% for multilevel disease ($p = 0.05$).[116] In one mixed IC and CLTI cohort of 236 patients and 289 limbs, infrapopliteal runoff did not affect either vessel patency or limb salvage after femoropopliteal stenting.[117] Iida et al. a studied a population of 884 patients and 1057 limbs undergoing endovascular revascularisation for CLTI due to isolated infrapopliteal disease. They identified the following risk factors: a small target artery diameter (< 3 mm), substantial lesion length (> 30 cm), lesion calcification and a lack of runoff below the ankle, as predictors of major adverse limb events (MALE). In this study, a MALE was defined as major amputation or any reintervention. Risk scores were calculated according to the presence of each factor, and a score between 0 and 4 was assigned. Categorisation of patients into low (score 0–1), moderate (score 2) and high-risk (score 3–4) groups stratified patients with respect to MALE. They obtained an AFS rate of 72.1%,

61.6% and 53%, for low, moderate and high-risk scores respectively at 2 years. Notably, even the TASC I classification was associated with MALE.[118] Hiramori et al. graded infrapopliteal runoff in 859 mixed IC and CLTI patients with endovascularly treated femoropopliteal lesions by contrast flow in angiography thus: no flow, slow flow, good flow. At three years, estimated freedom from MALE, defined as amputation or surgical revascularisation, was reported to be significantly lower in the no-flow group (36.6%), compared with the others (60.7–68.5%).[119] A retrospective review of 199 limbs in 117 diabetic patients by Toursarkissian et al. described pedal outflow as a foot score, comprising categorical degrees and lengths of stenoses or occlusions in the dorsal pedal artery and the plantar arteries as measured by angiography. The foot score was associated with graft patency and limb salvage. A score of ≥ 7 resulted in an amputation rate of 20%, and a score of < 7 in an amputation rate of 7%, during a mean follow-up of 14 months.[120] Using a foot score with the same cutoff, Baer-Bositis et al. studied 1134 patients whom had undergone crural endovascular therapy for CLTI. The authors found a significantly better 5-year estimated limb salvage for patients with a foot score < 7 (69%, standard error [SE] 4%) compared to those with ≥ 7 (45%, SE 6%). Moreover, AFS was significantly better for foot score < 7, compared with ≥ 7, at 48% (SE 5%) and 32% (SE 6%), respectively. Similar differences in mortality and AFS between the groups were seen even when comparing propensity-score-matched groups of 337 pairs of the patients. Total mortality was high, at 59%.[121] The effect of pedal arch patency on four-year AFS has been investigated separately. In a study of 154 CLTI patients whom underwent 167 infrapopliteal bypasses, no statistically significant difference was seen between patients with a completely patent (67.2%), incompletely patent (69.7%) and non-patent pedal arch (45.9%), possibly due to insufficient sample size.[122]

Although notable exceptions exist, most studies have found an increasing risk of death and/or amputation with increasingly atherosclerotic crural arteries, which probably reflects both an exaggerated propensity for CLTI and technically challenging revascularisations that arise from crural artery lesions.

2.5 Peripheral Pressure Measurements

In 1947, Burch described a portable volume pletysmograph[123] and shortly thereafter, Winsor used it to measure segmental systolic pressures of the extremities in patients with and without occlusive arterial disease, noting that lower extremity pressures were regularly higher than brachial pressures, but were notably diminished with arterial occlusion.[124] Later, Strandness and Bell used a mercury strain gauge pletysmograph, and predicted that pressure measurements would provide an objective measure for both diagnosis and efficacy of therapy for PAD.[125] Carter

found that the percentage of ankle systolic pressure in relation to brachial systolic pressure was sensitive in detecting occlusive arterial disease of the lower extremities, and thus effectively discovered the ABI.[126] Yao et al. similarly proposed the use of the ABI for diagnosis of arterial disease and follow-up of arterial reconstructions, while significantly simplifying the procedure by using a doppler probe instead.[127] Mercury-silastic strain gauge pletysmography is still considered the gold standard in peripheral pressure measurements, but has been largely replaced by photopletysmography and laser doppler flowmetry.[128,129]

ABI is defined as the ratio between systolic pressure in the anterior or posterior tibial artery and the brachial artery. ABI can easily be measured at a primary care setting, due to its simplicity and noninvasiveness.[130] Using a threshold value of 0.97, ABI has a sensitivity of 93–94% and a specificity of 84–88% for detecting hemodynamically significant (≥ 50%) lesions in the arteries of the lower limbs.[131,132]

In 1982, ABI was recommended for the diagnosis of PAD in the lower extremities for epidemiological studies.[133] The Cardiovascular Health Study (CHS) proposed that ABI was inversely related to the risk of CVD per se, in addition to the presence of CVD risk factors.[134] At present, ABI ≤ 0.9 is widely used for diagnosis and definition of PAD, with a sensitivity of 80–90% and a specificity of 90%. The higher of the two ankle artery pressures – i.e. the anterior or posterior tibial artery – in a limb should be used for diagnosis, whereas the lower pressure is recommended for prognostic assessment of CV risk,[135–137] as using the higher value will fail to identify up to 10% of high-risk patients.[138] The risk of overall and CV mortality in individuals with lower value ABI < 0.40 has been shown to be similar to that of those with higher value ABI < 0.40, regardless of the fact that these patients possess significantly fewer CV risk factors than their higher value counterparts.[139] A hemodynamically meaningful arterial stenosis involves significant luminal narrowing. Therefore ABI may not be useful for screening early atherosclerotic disease, but it is a very specific test for advanced disease.[140]

2.5.1 Abnormally Low ABI

ABI has been shown to be inversely and independently related to arterial disease in multiple vascular beds, such as the intima-medial thickness of the carotid and femoral bifurcations, in addition to disease burden of the coronary arteries.[141] The Rancho Bernardo Study revealed a U-shaped association between both abnormally high and low ABI with development of coronary calcium in women.[142] In the "Men born in 1914" study, a Swedish prospective cohort study of 439 diabetic men, the risk of MI was two-fold with ABI < 0.9, [143] and the age-only adjusted risk of CAD-related death was five-fold in 40–55-year old men with ABI ≤ 0.9.[144] The Honolulu Heart program showed that ABI < 0.8 increased the risk of CAD events in 2863

elderly men by almost three-fold (RR 2.7 [95% CI 1.6–4.5]).[145] An ABI ≤ 0.9 independently predicted fatal MI (RR 1.7 [95% CI 1.1–2.7]) at 12 years in the EAS[146] and cardiac death in diabetic patients (HR 1.7 [95% CI 1.1–2.5]) in the Fremantle Diabetes Study.[147] The Atherosclerotic Risk in Communities (ARIC) study found that, when adjusted for cardiovascular risk factors, ABI as a continuous variable was inversely related to the risk of CAD-related deaths and MI. It must be kept in mind that in that same study, APs of only one lower extremity were measured.[148] The population based CHS, on 5084 community-dwelling patients, showed an inverse association between ABI and the following: commonplace CV risk factors, increasing risk of MI, congestive heart failure, stroke and transient ischaemic attack (TIA). The normal and borderline ABI categories in that study were narrowly divided (≥ 1.0–< 1.5, ≥ 0.9–< 1.0, ≥ 0.8–< 0.9 and < 0.8).[134] In one prospective study of 1930 subjects, the 3-year risk of death from CAD approximately doubled for every 0.5 decrease in ABI.[149]

The increase in the risk of stroke with abnormal ABI has been proposed to be even greater than with known carotid stenosis,[150] and the literature generally supports the association of low ABI with an increased stroke risk. Although ABI appeared to be inversely associated with the risk of ischaemic stroke in the ARIC-study on 15792 individuals, low ABI was not independently predictive of the outcome.[151] A similar result was also obtained in the EAS.[146] In the Honolulu Heart Program study, ABI < 0.9 was independently associated with an increased adjusted risk of thromboembolic or haemorrhagic stroke (HR 2.0 [95% CI 1.1–3.5]) for 2676 men.[152] In a subgroup of the Framingham study, ABI < 0.9 was associated with a 2-fold risk of stroke or TIA (HR 2.0, 95% CI 1.1–3.7). [153] Thatipelli et al. reported a nearly 4-fold increase in the incidence of stroke in a study of CAD patients with concomitant PAD.[154] In one small study, ABI ≤ 0.9 was associated with a two-fold risk of recurrent stroke, MI or death in patients with previous ischaemic stroke or TIA.[155] An up to 12-fold risk of recurrent stroke was reported in another study of 176 patients with acute ischaemic stroke or TIA and without a previous PAD diagnosis, in which nearly 20% of patients with ABI ≤ 0.9 had recurrent stroke within 30 days.[156] A meta-analysis of 11 studies with 5374 patients associated low ABI with recurrent stroke (HR 1.7, 95% CI 1.1–2.6).[157] Another meta-analysis of 10 studies with 22355 subjects identified ABI < 0.9 as an independent predictor of both primary and recurrent stroke.[158] A population study of 4299 individuals found the risk of stroke to be inversely associated with ABI, and ABI < 0.9 was independently predictive of an almost four-fold risk (HR 3.9 [95% CI 2.4–6.4]).[159]

Given that abnormally low ABI is so clearly associated with age and other CV risk factors, and that the method of determining ABI varies across different studies, care must be taken when interpreting reports of the association of low ABI, defined in most studies as ≤ 0.9, with all-cause or CV mortality. Although Murabito et al.

did not find an independent association between abnormally low ABI and mortality in an elderly population of the Framingham study,[153] numerous other studies have done so (Table 12). The EAS reported that ABI ≤ 0.9 was associated with an increased adjusted risk of 5-year CV (RR 1.9) and all-cause mortality (RR 1.6), with a comparatively worse prognosis in patients with ABI ≤ 0.7.[160] In one 12-year analysis of the same cohort, however, even though the association between ABI and that of overall and CV mortality remained linear, an ABI ≤ 0.9 did not independently predict the outcome after adjustment for conventional CV risk factors in multivariable analysis.[146] In contrast, however, yet another analysis of the same cohort, ABI < 0.9 was indeed found to independently predict CV mortality (HR 1.5).[161] ABI < 0.9 independently predicted overall mortality and CV mortality in subjects with no known CVD at baseline (RR 1.6 and 2.0, respectively) by 6 years follow-up in the CHS. However, in subjects with prevalent CVD at baseline, only CV mortality was increased (RR 1.5).[140] After 10 years, ABI ≤ 1.0 for either lower limb independently predicted both overall and CV mortality, when compared to ABI 1.1–1.4, in the same study population.[162] In another analysis of the CHS-population, Aronow et al. obtained a similar risk of all-cause mortality for patients with ABI < 0.9 by using both multivariable (HR 1.5) and propensity adjustment (HR 1.6).[163] In the Strong Heart Study, Resnick et al. followed 4393 native Americans with a high prevalence of diabetes for over 8 years. The RR of all-cause mortality for ABI < 0.9 was 1.7 and for CV mortality 2.5, after a median follow-up of 8.3 years.[164] The Limburg Study was a prospective population study with 3649 subjects, in which 7-year CV mortality in subjects with ABI < 0.95 and subjects with ABI ≥ 0.95 were 16.2% and 5.1%, respectively and the estimated overall mortality with ABI < 0.95 was 27.5%.[165] In a later publication, the same authors were able to show that the hazard for all-cause mortality (HR 1.4) and CV mortality (HR 1.5) were increased in the asymptomatic PAD population with ABI < 0.95, but not in patients with PAD symptoms, when compared with healthy subjects. However, only 117 subjects in the study had symptomatic PAD.[166] The population-based Multi-Ethnic Study of Atherosclerosis of 6647 subjects with no CVD at baseline, found ABI < 1.00 was independently associated with a composite end point of incident CAD, stroke or CV death.[167] With a mean follow-up of 4.3 years in a prospective cohort study of 1492 women aged 65 years or older, increased risk of all-cause mortality (RR 3.1) and CV mortality (RR 4.0) were associated with ABI ≤ 0.9.[168] In the 'Men born in 1914' study, ABI < 0.9 predicted all-cause mortality at 8 years (RR 2.4), when adjusted for age, smoking and hyperlipidaemia.[143] A study of 2023 middle-aged men reported age-only adjusted RR for all-cause mortality in men with ABI ≤ 0.9, compared to those with normal ABI, was 2.8, and for CV death, 4.2.[144] In a study of 395 CAD patients with coincidental PAD and varying degrees of ischaemia, ABI < 0.9 was associated with all-cause mortality (HR 2.3) at follow-up of 4.7 years,.[154]

Table 12. Abnormally low ABI; all-cause and CV mortality.

Author year	Study (n)	Group (n)	All-cause mortality (95% CI)	CV mortality (95% CI)	Follow-up	Only adjusted for
Vogt 1993	Multicenter study of osteoporotic fractures (1492, female)	ABI ≤ 0.9 (82, female)	RR 3.1 (1.7-5.5)	RR 4.0 (1.7-9.1)	4.3 years (average)	
Ögren 1993	Men born in 1914 (477, male)	ABI < 0.9 (60, male)	RR 2.4 (1.5-3.9)	-	8 years	Smoking, HA, hyperlipidemia
Kornitzer 1995	Asymptomatic middle-aged men (2023, male)	ABI ≤ 0.9 (77, male)	RR 2.8 (1.4-5.5)	RR 4.2 (1.7-10.5)	(n/a)	Age
Leng 1996	Edinburgh artery study (1582)	ABI ≤ 0.9 (288)	RR 1.6 (1.1-2.2)	RR 1.9 (1.2-3.0)	5 years	
Newman 1999	Cardiovascular health study (5714)	ABI < 0.9, no CVD (409)	RR 1.6 (1.2-2.1)	RR 2.0 (1.2-3.4)	6 years	
		ABI < 0.9, with CVD (359)	n.s.	RR 1.5 (1.1-2.2)		
Aronow 2009	Cardiovascular health study (5630)	ABI < 0.9 (767)	HR 1.5 (1.4-1.7)	-	7.5 years (median)	
		ABI < 0.9 (679)*	HR 1.5 (1.2-1.8)	-		*Propensity-matched
Murabito 2003	Framingham study (674)	ABI < 0.9 (141)	n.s.	-	4 years	Age, sex, CVD
Hooi 2004	Limburg PAOD study (3070)	ABI < 0.95, asymptomatic (245)	HR 1.4 (1.1-1.8)	HR 1.5 (1.1-2.2)	7.2 years (mean)	
		ABI < 0.95, symptomatic (117)	n.s.	n.s.		
Lee 2004	Edinburgh artery study (1592)	ABI ≤ 0.9 (245)	RR 1.4 (1.2-1.7)	RR 1.8 (1.3-2.5)	12 years	Age, sex
			RR 1.3 (1.1-1.6)	RR 1.5 (1.1-2.1)		Age, sex, DM, CHD
			n.s.	n.s.		
Resnick 2004	Strong Heart study (4393)	ABI < 0.9 (216)	RR 1.7 (1.3-2.1)	RR 2.5 (1.7-3.6)	8.3 years (mean)	
Wild 2006	Edinburgh artery study (1467)	ABI < 0.9 (258)	-	HR 1.5 (1.2-2.1)	15 years	
Li 2007	Patients with type 2 diabetes (1674)	ABI < 0.9 (531)	RR 1.9 (1.3-2.7)	RR 3.2 (1.7-6.1)	13 months	
Thatipelli 2007	CHD patients (395)	ABI < 0.9 (341)	HR 2.3 (1.4-4.1)	-	4.7 (mean)	
Sutton-Tyrrell 2008	Health, aging, and body composition study (2886)	ABI ≤ 0.9 (383)	RR 1.6 (1.3-2)	2.2 (1.6-3.0)	6.7 years (mean)	
Suominen 2010	PAD outpatients (2159)	ABI ≤ 0.9 (1381)	OR 1.8 (1.3-2.3)	OR 1.7 (1.2-2.4)	3.3 years (average)	
Abbott 2012	BARI 2D trial subgroup (2368)	ABI ≤ 0.9 (430)	RR 1.7 (1.3-2.2)	-	5.2 years (median)	
Hanssen 2012	Hoorn study (624)	ABI < 0.9 (65)	RR 2.0 (1.5-2.8)	RR 2.6 (1.5-4.4)	17.2 years (median)	
Potier 2015	REACH registry subgroup (6986)	ABI ≤ 0.9 (3322)	HR 2.0 (1.7-2.4)	HR 2.0 (1.6-2.4)	4 years	
Nishimura 2017	IMPACT-ABI study subgroup (1500)	ABI < 0.9 (138)	HR 1.58 (1.02-2.45)	-	5 years (mean)	

Due to reasons that will be outlined later, it might be argued that the prognostic capability of abnormally low ABI could potentially suffer in a population of diabetics. On the other hand, there are a number of studies that show the predictive usefulness of ABI even in diabetic patients. A subgroup of the Bypass Angioplasty Revascularisation Investigation 2 Diabetes (BARI 2D) trial included 2368 diabetic patients with a median follow-up of 5.2 years. In that study, RR of 1.7 for all-cause death in patients with ABI ≤ 0.9 was reported.[169] After 6.7 years follow-up of 2886 physically adept persons aged 70–79 years in a community-based study, RRs of all-cause and CV mortality in patients with ABI ≤ 0.9 were 1.6 and 2.2, respectively.[170] In a study of 1647 Chinese type 2 diabetics, ABI ≤ 0.9 independently predicted short-term overall mortality (RR 1.9) and CV mortality (RR 3.2).[171] After a median of 17.2 years of follow-up in the population based Hoorn study of 624 participants, adjusted RRs of all-cause and CV mortality with ABI < 0.9 were 2.0 and 2.6, with no difference between diabetic and non-diabetic patients.[172] A total of 6986 patients of the Reduction of Atherothrombosis for Continued Health (REACH) registry were studied by Potier et al. They found that ABI ≤ 0.9 was independently associated with a HR of 2.0 with both overall and CV mortality, although the population had a substantial proportion of diabetics (41%), and that there was no heterogeneity according to diabetic status regarding the association.[173] Zobel et al. followed 200 type 2 diabetics with microalbuminuria for a median of 6.1 years in a prospective study. After adjusting for traditional CV risk factors, a 1 SD decrease of ABI as a continuous variable increased the HR of all-cause death to 1.4 (95% CI 1.1–1.6).[174] In a subgroup of 1500 patients from the Impressive Predictive Value of Ankle-Brachial Index for Very Long Term Outcome in Patients with Cardiovascular Disease (IMPACT-ABI) study with mild renal insufficiency (eGFR 60–89 ml/min), ABI < 0.9 independently predicted MACE (HR 2.3 [95% CI 1.3–3.9]) and death (HR 1.58).[175]

A meta-analysis of 11 longitudinal studies with a combined total of 44590 subjects pooled age and sex-adjusted estimates for all-cause mortality (RR 2.4 [95% CI 1.7–3.3]) and CV mortality (RR 3.3 [95% CI 2.1–5.3]) with ABI < 0.9.[176] Another meta-analysis pooled 19 studies that reported outcome with PAD as identified by ABI screening, then calculated pooled HRs of 3.0 (95% CI 2.2–4.1) for all-cause mortality and 2.4 (95% CI 1.9–2.9) for CV mortality. Most studies included in this analysis used a threshold ABI of < 0.90.[177] In another meta-analysis, 43 observational cohort studies that totalled 94254 participants, found that ABI < 0.9 was associated with significant pooled risks of all-cause mortality (RR 2.5 [95% CI 2.3–2.8]) and CV mortality (RR 2.9 [95% CI 2.7–3.2]).[178]

Changes in ABI may also reflect disease progression in other vascular beds. A three-fold (HR 3.0, 95% CI 1.3–6.7) independent risk of death was observed in conservatively treated PAD patients with a 6–20% decline in resting ABI, with the

greatest risk in patients with > 20% decline of resting ABI (HR 3.3, 95% CI 1.5–7.2). A similar, but less pronounced risk increase was seen with declining post-exercise ABI.[179] Overall, the prognostic accuracy of post-occlusion or exercise-ABI does not appear to differ from that of resting ABI.[180]

The evidence in the literature of abnormally low ABI as an indicator for PAD that predicts adverse outcome both at the level of the general population, and within well-defined high-risk cardiovascular groups, is overwhelming. The RR of overall mortality with abnormally low versus normal ABI varies between 1.4 and 3.1 across studies, and that of CV mortality between 1.5 and 4.2.

2.5.2 Abnormally High ABI

Over 20% of patients with PAD-associated comorbidities and risk factors,[181] and up to 29% of CLTI patients with low TBI have normal ABI.[182] A major factor causing this discrepancy is the stiffening of the ankle arteries due to medial arterial calcification (MAC), which may render leg arteries entirely incompressible at reasonable pressures, which makes it impossible to determine an ABI. Ankle pressure may also be moderately elevated so that ABI is overtly high (> 1.3–1.4). MAC may even result in a normal ABI in the presence of significant PAD. MAC is prevalent in diabetic patients with foot ulcers, especially in those with neuropathy and a long duration of diabetes.[183]

PAD may be present in a significant proportion of patients with MAC. It was reported that 56% of patients with ABI > 1.4 had PAD in a study whereby over 90% of the patients were diabetic.[184] A study of 1762 vascular surgical outpatients of whom a third had diabetes reported the percentage with ABI ≥ 1.30 was 8.4%. Over 60% of those with an ABI ≥ 1.30 had a TBI < 0.60, which implicated PAD.[185] In a later publication of 2159 subjects in the same setting, the incidence for ABI ≥ 1.3 was 8.6%.[186] When compared, this proportion of patients with MAC was similar to that reported in the high CV risk population of the Strong Heart Study,[164] and almost twice that of the population-based ARIC study.[187] Potier et al. proposed that occlusive PAD as diagnosed by DUS may be present in over half of diabetics with normal ABI,[188] and that the sensitivity of ABI in detecting PAD is particularly reduced in diabetic patients with neuropathy, foot ulcers or high CV risk.[189] In addition to diabetic patients, the sensitivity of ABI < 0.9 in detecting PAD appears to be lower in patients with: old age, distal lesions and mild stenoses.[190] Abnormally high ABI has further been associated with: renal insufficiency,[191] smoking, dyslipidaemia and obesity.[192] A 20-year longitudinal study of 4553 Pima Indians reported that the prevalence of radiologically detected MAC was age-dependent. MAC was found to primarily affect arteries of the feet and to a lesser extent, those of the calves and thighs in this population. MAC was also found to be more prevalent

in nondiabetic men than women and equally frequent in diabetic men and women. The degree of hyperglycaemia and duration of diabetes were associated with the development of radiological MAC, but in this study, age, sex and renal function were not.[193]

The majority of studies reporting all-cause or CV mortality in relation to abnormally high ABI show a positive independent association, but there are exceptions (Table 13). Velescu et al. followed 5679 individuals for a median of 6.2 years in the population based REGICOR study. Those authors reported that ABI ≥ 1.40 was predictive of overall and CV mortality after adjusting for age and sex, but only of overall mortality after adjusting for some CV risk factors (HR 3.3 [95% CI 1.9–5.5). When traditional CV risk factors were taken into account, significance was lost. The total number of participants in the study was large but only 162 had ABI ≥ 1.40.[194] Although the ARIC study used ABI measured for only one leg, the number of participants eligible for a median 12-year follow-up was a remarkable 14777. In this setting, the ARIC study found no association between abnormally high ABI and a composite end point of MI, stroke or CV death. In this community based study, the prevalence of ABI > 1.3, > 1.4 and > 1.5 in one lower extremity was 5.5%, 1.2% and 0.37%, respectively. In the same study, a high ABI was equally prevalent in diabetics and non-diabetics alike.[187] The population-based Multi-Ethnic Study of Atherosclerosis is frequently quoted as having showed that the risk of incident CAD, stroke or CV death was high in individuals with ABI ≥ 1.40, however the independent association was not statistically significant.[167] Hendriks et al. studied a large cohort of 7538 subjects with a high risk of, or actual prevalence of CVD and ABI > 0.9. In this study, 336 participants had an ABI ≥ 1.40 or incompressible ankle arteries, which independently predicted MI. The authors found no significant difference in either CV or overall mortality between the groups.[195]

Table 13. Abnormally high ABI; all-cause and CV mortality.

Author year	Study (n)	Group (n)	All-cause mortality (95% CI)	CV mortality (95% CI)	Follow-up	Only adjusted for
Resnick 2004	Strong Heart study (4393)	ABI > 1.4 (404)	RR 1.8 (1.5-2.1)	RR 2.1 (1.5-2.9)	8.3 years (mean)	
O'Hare 2006	Cardiovascular health study (5748)	ABI > 1.4 (66)*	HR 1.6 (1.1-2.3)	n.s.	11.1 years (median)	
Aboyans 2005	CABG patients (1022)	ABI > 1.5 (124)	HR 2.1 (1.2-3.6)	HR 2.6 (1.3-5.2)	4.4 years	
Sutton-Tyrrell 2008	Health, aging, and body composition study (2886)	ABI > 1.3, compressible (141)	n.s.	n.s.	6.7 years (mean)	
		ABI > 1.3, non-compressible (63)	RR 1.8 (1.2-2.7)	RR 2.6 (1.4-4.9)		
Suominen 2010	PAD outpatients (2159)	ABI ≥ 1.3 (185)	OR 2.3 (1.5-3.4)	n.s.	3.3 years (average)	
		ABI > 1.5 (N/A)	OR 3.4 (1.9-6.1)	OR 3.1 (1.6-5.6)		
Abbott 2012	BARI 2D trial subgroup (2368)	ABI > 1.3, compressible (182)	n.s.	-	5.2 years (median)	
		ABI > 1.3, non-compressible (139)	RR 1.9 (1.3-2.8)	-		
Potier 2015	REACH registry subgroup (6986)	ABI ≥ 1.3, diabetic (85)	HR 2.1 (1.2-3.8)	HR 2.13 (1.03-4.44)	4 years	
		ABI ≥ 1.3, nondiabetic (119)	n.s.	n.s.		
Hendriks 2016	SMART study subgoup with ABI > 0.9 (7542)	ABI ≥ 1.4 (336)	n.s.	n.s.	6.9 years (median)	
Velescu 2017	REGICOR study (5679)	ABI ≥ 1.4 (162)	HR 2.0 (1.3-2.9)	HR 3.1 (1.52-6.48)	6.2 (median)	Age, sex
			HR 3.3 (1.9-5.5)	n.s.		REGICOR risk
			n.s.	n.s.		

* Reference ABI 1.11–1.2.

The Strong Heart Study showed the association between ABI and outcome was U-shaped, with high mortality both in patients with low and high ABI. The RR of all-cause mortality for ABI > 1.4 was 1.8, and for CV mortality, it was 2.1.[164] Pooled data in a meta-analysis of 16 studies with nearly 50000 individuals whom represented the general population, showed the association between ABI and overall and CV mortality to be similarly "reverse J-shaped", with risk stratification according to ABI.[196] A dissociation between high ABI and mortality in non-diabetics was reported by Potier et al. in a subgroup analysis of 6986 patients of the REACH registry, for which over 40% of patients had diabetes. ABI ≥ 1.3 independently predicted mortality (HR 2.6) and CV mortality (HR 2.6) in diabetic patients, but not in non-diabetics or the pooled population. The evident association of low ABI and mortality, on the other hand was not affected by diabetes.[173] Hiramori et al. noted a crude U-shaped association of ABI with MACE and overall mortality in a retrospective study of 1851 percutaneous coronary intervention patients. They reported a 4-year crude mortality for low (< 0.9), borderline, normal (1.0–1.4) and high ABI of 22%, 12%, 6.9% and 29%, respectively. However, they did not report multivariable analysis for mortality, but for MACE, only a low ABI was independently associated with the outcome.[197]

The CHS followed-up patients for up to 10 years and showed ABI > 1.4 to be associated with an increased risk of all-cause mortality (HR 1.6) but not of CV mortality.[162] MAC, as defined by ABI > 1.5, independently predicted overall (HR 2.1) and CV mortality (HR 2.6) in a group of patients undergoing CABG.[43] In another study on CABG patients, Le Bivic et al. found that ABI of either < 0.9 or > 1.4, as a marker for PAD, independently predicted all-cause mortality (HR 1.5 [95% CI 1.2–1.9]). They also found that the increase in risk was significant regardless of the method used for calculating ABI.[30] In a later study by Suominen et al., it was reported that both ABI ≤ 0.9 and ABI > 1.5 independently predicted all-cause mortality (OR 1.8 and 3.4, respectively) and CV mortality (OR 1.7 and OR 3.1, respectively). Furthermore, there was meaningful stratification of all-cause mortality according to the highest and lowest categories of ABI. Although ABI ≥ 1.3 independently predicted the risk of all-cause mortality (OR 2.3), the increase in risk for CV mortality was not significant after multivariable adjustment.[186] In another referral outpatient study, Arain et al. retrospectively assessed 16493 individuals with suspected PAD, of whom a significant 17% (n = 2781) had poorly compressible leg arteries (PCA) as defined by ABI ≥ 1.40 or AP > 255 mmHg, in at least one extremity. Notably, patients with borderline normal ABI (0.91–0.99 and 1.31–1.39) were excluded, which created sharply defined groups of patients with low ABI, particularly normal ABI and PCA. Mean estimated 5-year survival in patients with low ABI was 79%, with normal ABI 86%, and with PCA 74%. Multivariable analysis, after adjustment for traditional CVD risk factors and CLTI, revealed the HR for all-cause mortality with low ABI was 1.5 (95% CI 1.4–1.6)

and with PCA, 1.8 (95% CI 1.6–2.0).[198] In a 3-year follow-up series of 284 CLTI patients, ABI > 1.4 was associated with increased unadjusted risks of mortality, major amputation, and amputation or death. Multivariable analysis was only performed for the risk of MACE (HR 1.65, 95% CI 1.02–2.70) in this study.[199]

A meta-analysis of 18 studies assessed the association of high abnormal ABI with all-cause and CV mortality of 9646 subjects that represented the general population. The study reported pooled risk ratios for overall and CV mortality of 1.5 (95% CI 1.2–1.8) and 1.8 (95% CI 1.4–2.4), respectively. For the subgroup of subjects with established or suspected CVD, both pooled risk ratios were 1.6 (95% CI 1.1–2.2 and 1.2–2.1, respectively).[200] Another meta-analysis of 43 observational cohort studies included altogether 94254 participants and reported the risk of all-cause mortality was high in the subgroup with abnormally high ABI (RR 3.1 [95% CI 2.9–3.4]). Unfortunately, the effect of high ABI on CV mortality could not be assessed in that meta-analysis.[178]

The definition and degree of MAC appears to play a role in outcome, as MAC can manifest itself as either high but measurable ABI or as entirely incompressible arteries. The BARI 2D trial associated both ABI ≤ 0.9 and incompressible leg arteries in type 2 diabetic patients with CAD, and found similar rates of 32% and 34%, and corresponding risks (RR 1.4 [95% CI 1.1–1-7] and RR 1.5 [95% CI 1.1–2.1]) of MACE at 5 years. The RR of all-cause mortality was higher (1.9 [95% CI 1.3–2.8]) for incompressible arteries than for low ABI. Compressible arteries with ABI > 1.3 did not increase the adjusted risks, compared to normal ABI.[169] Sutton-Tyrell et al. also divided patients with abnormally high ABI into those with non-compressible arteries and those with measurable, but abnormally high ABI ≥ 1.31. In concordance to that found in the BARI 2D trial, patients with high but definable ABI did not have a greater risk of either all-cause or CV mortality than those with normal ABI, and the risk was highest in those with non-compressible arteries (RR 1.8 [95% CI 1.2–2.7] and RR 2.6 [95% CI 1.4–4.9], respectively).[170]

Studies that show an association between abnormally high ABI and increased mortality outnumber those that do not, though results are not entirely consistent. MAC per se does not appear to cause a poor outcome, but rather it is due to the underlying PAD it is masking. As MAC is especially prevalent in diabetic and high-risk CV patients, it appears to hamper the ability of ABI to be used for providing accurate prognostic data in this population. This concept was illustrated by Aboyans et al., who retrospectively classified 403 diabetic patients into groups of normal, occlusive PAD (ABI ≤ 0.9), isolated MAC with no occlusive PAD (ABI ≥ 1.40), and mixed disease with both MAC and occlusive PAD (ABI ≥ 1.40), as detected by DDUS. Survival analysis showed that CVD event-free survival was poorest in the occlusive PAD and mixed disease groups. After adjustment for risk factors, only occlusive PAD could be shown to predict a composite end point of mortality, MI or

stroke (HR 2.2 [95% CI 1.2–4.2]).[184] Similarly, Suominen et al. demonstrated in patients with ABI ≥ 1.3 that a TBI < 0.60 independently predicted all-cause (OR 2.21 [95% CI 1.01–4.85]) and CV mortality (OR 4.9 [95% CI 1.5–16.0]).[186]

2.5.3 Borderline ABI

O'Hare et al. reported long-term results from the CHS that did not show a truly linear stratification of overall or CV mortality with ABI, using either the limb with the lowest or highest value, after full adjustment for confounding factors. A significant finding of their study, however, was the increased risk for both outcomes in individuals with borderline ABI in the low normal range between 0.91 and 1.00, compared to ABI between 1.11 and 1.20. Moreover, this increase was even more pronounced in the limb with the higher ABI. For this contralateral ABI, the risk of CV death was slightly, but significantly higher even in patients with ABI 1.01–1.10.[162] Subsequent recommendations by the ACC and the AHA state that borderline ABI (0.91–0.99) should be treated similar to low ABI as far as CV risk is concerned.[196,201] Both low (≤ 0.9) and borderline (0.91–0.99) ABI have been independently associated with heart failure in patients hospitalised for CVD.[202] In a registry study of 4756 high-risk patients, borderline ABI (0.91–1.00) was associated with CVD risk factors, such as diabetes, low left ventricular ejection fraction and decreased kidney function, and was independently associated with overall mortality (HR 2.3 [95% CI 1.3–4.0]) and CV mortality (HR 3.4 [95% CI 1.6–7.8]).[203] After a mean of 4.8 years follow-up, in 3051 hospitalised cardiology patients enrolled in the Japanese IMPACT-ABI study, patients with ABI ≤ 0.9 and those with borderline ABI (0.91–0.99) had significantly higher adjusted risks of MACE than those with ABI 1.00–1.40 (HR 1.9, 95% CI 1.4–2.6 and HR 1.54, 95% CI 1.03–2.29, respectively). The incidence of CV death in low, borderline and normal ABI-groups was 26.2%, 18.7% and 8.9% ($p < 0.0001$), respectively.[204]

In an interesting study, 1245 patients with normal ABI (1.00–1.40) were compared according to normal post-exercise ABI drop (≤ 20%) or increase. Prior to this, patients with normal resting ABI and a post-exercise drop of > 20% due to PAD had been excluded. The patients with post-exercise ABI increase were more likely to suffer from a composite end point of death or MACE (adjusted HR 1.7, 95% CI 1.1–2.5). Propensity score matching in the same study, after adjustment for risk factors, gave similar results, with a HR of 1.8 (95% CI 1.2–2.8). The significance and mechanism of this finding is unclear, but the authors consider endothelial-dysfunction driven lack of appropriate vasoconstriction in response to physical exertion a possible explanation. As there was suspicion of MAC having a role in the results, the subgroup of 120 patients with ABI 1.3–1.4 was excluded, but the adjusted hazard remained high (HR 1.7 [95% CI 1.1–2.6]).[205]

2.5.4 ABI Across the Spectrum

Attempts have been made to stratify risk according to varying ABI within the abnormal range. Most of such studies report increased all-cause or CV mortality with extremely low ABI, and a number of studies show linear worsening of outcome with decreasing ABI, though there are inconsistencies (Table 14). In 1989, Howell et al. observed 247 referral patients categorised by ABI and reviewed them for 6-year outcomes. Low ABI (≤ 0.30) was associated with increased mortality, 64% at 6 years. ABI in the lower spectrum was also associated with amputation, with 32% of patients with ABI ≤ 0.30, and 13% with ABI 0.31–0.49 amputated. The association of low ABI with the incidence of MI or stroke was not significant. All-cause mortality in the study was 28%, of which 57% was accounted for by CV-mortality.[206] Amrock et al. observed 647 patients with ABI ≤ 0.9. Stratification into ABI < 0.5, 0.50–0.69 and 0.70–0.90 failed to show any significant difference in overall mortality between the groups after multivariable adjustment. The hazard for CV mortality was high in patients with ABI < 0.50 (HR 2.6), compared to ABI 0.70–0.90, with no significant difference between the groups with higher ABI.[207] Stratification of abnormal ABI (< 0.92) in a retrospective study of 422 PAD patients revealed that ABI ≤ 0.3 was associated with a HR of 1.8 for 4.3-year mortality, comparing to those with ABI 0.5–0.91. The difference in hazard between the latter group and ABI 0.31–0.49, was not significant.[130] In the Limburg Study, the risk of overall mortality and CV mortality was over two-fold with ABI < 0.70, compared to those with ABI ≥ 0.95. With ABI between 0.70 and 0.94, CV mortality was not significantly higher than with normal ABI.[165]

McKenna reported an increasing risk of death from CVD with decreasing ABI in a cohort of 744 patients. Patients with ABI > 1.5 were excluded, but ABI was otherwise linearly associated with mortality in diabetic and non-diabetic patients, with 5-year mortality of 66% and 10% with ABI < 0.4 and > 0.85, respectively. Furthermore, 71% of deaths were classified as cardiovascular and ABI was inversely correlated with the incidence of MI. Multivariable analysis revealed that ABI 0.4–0.85 resulted in a RR of death of 2.0, and ABI < 0.4 in a RR of 3.4, compared to ABI > 0.85.[208] In 1930 referral patients followed for over 3 years, age-adjusted mortality was similar for controls (ABI > 0.90) and ABI 0.71–0.90. RR of death was higher with ABI 0.51–0.70, and further increased with ABI ≤ 0.5. For men, ABI categories inversely correlated with standardised mortality ratios. For women, this correlation was significant from moderate to severe disease (ABI 0.51–0.70 to ABI ≤ 0.5). The majority of deaths in the cohort, 60%, were due to CV causes.[149] Diehm et al. in the prospective getABI cohort study of 6821 primary health care subjects aged ≥ 65 years, were able to show a stratification of risk for overall mortality for low abnormal ABI, when unconventionally using ABI ≥ 1.1 as the reference. There was no significant difference in mortality between the reference

group and that of normal (0.9–1.0) ABI. One group was defined as "major PAD" by ABI < 0.5 or by previous revascularisation or amputation. The adjusted 3-year hazard of all-cause death was greatest for this group, followed by ABI 0.5–0.6 and by ABI 0.7–0.8.[209] In a Chinese study, a total of 3210 type 2 diabetic patients were grouped by ABI into categories ≤ 0.4 and 0.41–0.90, and then compared to ABI 1.0–1.4. The adjusted RR of all-cause and CV mortality with ABI ≤ 0.4 was 3.1 and 4.8, for ABI 0.41–0.90, 1.5 and 2.0, respectively.[210] Hyun et al. showed a U-shaped age-and-sex adjusted association between ABI and the hazard of CV death in 469 PAD outpatients, but after adjusting for multiple risk factors, ABI > 1.30 was no longer independently associated with the outcome. Notably, there were only 14 patients with ABI > 1.30 in that study. Fully adjusted HRs for CV mortality were 1.9 for ABI 0.60–0.89 and 3.4 for ABI < 0.60, compared to normal ABI.[211]

Table 14. ABI across the spectrum; all-cause and CV mortality.

Author (year)	Study, population	Reference	Group, (n)	All-cause mortality (95% CI)	CV mortality (95% CI)	Follow-up
McKenna (1991)	PAD outpatients (744)	ABI ≥ 0.85	0.4 ≤ ABI < 0.85, (n/a)	RR 2.0 (1.3-3.0)	-	3.3 years (median)
			ABI < 0.4, (n/a)	RR 3.4 (2.2-5.2)	-	
Vogt (1993)	Study of osteoporotic fractures (1492, female)	ABI > 1.0	0.9 < ABI ≤ 1.0, (169)	n.s.	-	4.3 years (average)
			0.8 < ABI ≤ 0.9, (37)	RR 5.3 (2.6-10.9)*	-	
			ABI ≤ 0.8, (45)	RR 4.0 (2.0-8.3)*	-	
Vogt (1993)	Referral patients (771 male, 681 female)	ABI > 0.90 (male)	ABI 0.71-0.90, (n/a)	n.s.	-	3.2 years (median)
			ABI 0.51-0.70, (n/a)	RR 1.6 (1.2-2.2)*	-	
			ABI ≤ 0.50, (n/a)	RR 2.0 (1.4-2.7)*	-	
		ABI > 0.90 (female)	ABI 0.71-0.90, (n/a)	n.s.	-	3.1 years (median)
			ABI 0.51-0.70, (n/a)	RR 1.7 (1.2-2.4)*	-	
			ABI ≤ 0.50, (n/a)	RR 2.1 (1.5-3.1)*	-	
McDermott (1994)	PAD patients with ABI < 0.92 (422)	ABI 0.50-0.91	ABI 0.31-0.49, (105)	n.s.	-	4.3 years
			ABI ≤ 0.30 (71)	HR 1.8 (1.2-2.9)	-	
Hooi (2002)	Limburg Study (3634)	ABI ≥ 0.95	0.70 ≤ ABI < 0.95, (310)	n.s.	n.s.	7.2 years (median)
			ABI < 0.70, (148)	HR 2.1 (1.6-2.8)	HR 2.3 (1.7-3.1)	
Diehm (2006)	getABI study (6821)	ABI ≥ 1.1	0.9 ≤ ABI < 1.1, (3414)	n.s.	-	3 years
			0.7 ≤ ABI < 0.9, (800)	HR 1.7 (1.2-2.4)	-	
			0.5 ≤ ABI < 0.7, (214)	HR 3.1 (2.0-4.7)	-	
			ABI < 0.5, (212)**	HR 3.6 (2.4-5.4)	-	
Li (2010)	China ABI Cohort Study (3210, type 2 diabetics)	ABI 1.00-1.4	ABI 0.91-0.99, (507)	n.s.	n.s.	3.1 years (mean)
			ABI 0.41-0.90, (887)	RR 1.5 (1.2-2.0)	RR 2.0 (1.5-2.8)	
			ABI ≤ 0.4, (82)	RR 3.1 (1.9-5.0)	RR 4.8 (2.7-8.4)	
Suominen 2010	PAD outpatients (2159)	0.9 < ABI < 1.3	ABI ≤ 0.5 (n/a)	OR 2.4 (1.8-3.2)	OR 2.3 (1.5-3.4)	3.3 years (average)
			0.5 < ABI ≤ 0.7 (n/a)	OR 1.5 (1.1-2.0)	n.s.	
			0.7 < ABI ≤ 0.9 (n/a)	n.s.	n.s.	
			1.3 ≤ ABI ≤ 1.5 (n/a)	OR 2.3 (1.3-4.2)	n.s.	
			ABI > 1.5 (n/a)	OR 3.4 (1.9-6.1)	OR 3.1 (1.6-5.9)	
Hyun (2014)	PAD outpatients (469)	ABI 0.90-1.30	ABI > 1.30, (14)	-	n.s.	7 years (median)
			ABI 0.60-0.89, (160)	-	HR 1.9 (1.2-2.9)	
			ABI < 0.60, (106)	-	HR 3.4 (2.2-5.3)	
Tanaka (2016)	Cardiovascular patients (4756)	ABI 1.01-1.39	ABI 0.91-1.00, (324)	HR 2.3 (1.3-4.0)	HR 3.4 (1.6-7.8)	2.8 years (average)
Amrock (2017)	PAD patients with ABI ≤ 0.9 (647)	ABI 0.70-0.90	ABI 0.50-0.69, (155)	n.s.	n.s.	7.8 years (median)
			ABI < 0.50, (45)	n.s.	HR 2.6 (1.3-5.2)	

*Only adjusted for age; **Or history of revascularisation or amputation.

A number of studies have showed evidence of stratification of all-cause or CV mortality across the spectrum of abnormally low ABI, such that mortality has increased with decreasing ABI. Yet, whereas a very low ABI has consistently been associated with poor outcome, differences are less consistent within the upper spectrum of abnormally low ABI.

2.5.5 Ankle Pressure

ABI has proven value in both detecting PAD and predicting outcome, whereas AP has primarily been used for assessing the viability of limbs that are affected by the disease. This was suggested by Ouriel et al., who used an AP cutoff of 60 mmHg to correctly identify limb viability in 86% and amputation in 77% of 133 cases.[131] Some studies have supported that rationale, whereas others clearly have not, and small observational studies comprise the majority of available literature. The relationship between AP and foot viability was first proposed in the 1970's, with the observed failure of forefoot amputations to heal with AP < 35–55 mmHg.[212,213] An AP of 70 mmHg was initially suggested as the threshold for healing for below-the-knee amputations.[214] In a study by Baker and Barnes, forefoot amputations failed to heal in all patients with AP < 60 mmHg, whereas 86% healed with AP > 70 mmHg.[215] A more recent study of 602 non-revascularised diabetic ulcer patients with TP < 45 mmHg showed a healing rate of 50% without major amputation. In this group of patients that met CLTI criteria, a crude association of AP > 50 mmHg with increased probability of healing, with or without a minor amputation was observed (OR 2.4 [95% CI 1.3–4.7]), but no multivariable analysis was undertaken in this study.[216] In a study of 134 patients, of whom 76% were diabetic, no forefoot amputations healed for the AP ≤ 50 mmHg group. However, there was no association between higher AP and healing reported in the same study either, which was possibly due to falsely elevated AP caused by MAC.[217]

The predictive accuracy of AP for forefoot ulcer or gangrene healing in diabetic patients was poor in one study,[218] but good in another.[219] In the aforementioned study by Baker and Barnes, although the majority of forefoot amputations healed in patients with AP > 70 mmHg, the mean AP in diabetic patients with non-healing amputations was 79 mmHg. Infection and distal lesions aside, the authors considered the possibility of increased vessel wall rigidity in diabetic patients exacerbated the recorded pressures.[215] In the IN.PACT DEEP trial of 358 CLTI patients, AP meeting CLTI criteria was found in only 16% of subjects.[182] Similarly, AP ≤ 50 mmHg did not properly classify 83% of limbs with Fontaine III-IV CLTI as critically ischaemic in a 49-patient study.[220] In a small 52-patient series with a majority of diabetic patients (73%), Mehta el al. found no significant association between AP and healing of forefoot amputations.[221] A study of 309 patients with CLTI and tissue loss

reported that 27% of affected limbs underwent amputation. In that study, even though AP was significantly higher in diabetic patients, their RR for amputation was almost two-fold compared to non-diabetics.[26] A 2511-person prospective cohort study found no significant association between low AP and increased risk of major amputation in diabetic patients with neuroischaemic ulcers.[222] A subgroup analysis of the COPART trial also failed to associate AP with amputation.[63] The combination of ABI < 0.5 and AP < 50 mmHg appeared, however, more useful than TP in predicting major amputation in patients with diabetic foot ulcers, according to a recent systematic review.[223]

Two studies have demonstrated that low AP may be associated with increased mortality (Table 15). Sartipy et al. used AP ≤ 70 mmHg alone as the criterion for severe limb ischaemia, in a population-based study with 5080 participants and a 10-year follow-up. Age-only adjusted HRs for all-cause mortality (2.3) and CV mortality (3.5) were higher for AP ≤ 70 mmHg than for controls: patients with asymptomatic PAD or IC with ABI < 0.9 but AP > 70 mmHg.[47] At 2-years follow-up of the BASIL trial cohort of 452 CLTI patients, an AP < 50 mmHg gave a 2.6 HR of death, when compared to patients with an AP ≥ 50 mmHg and no tissue loss. Adjusted mortality in patients with an AP ≥ 50 mmHg and tissue loss did not significantly differ from those without tissue loss.[110]

The association of AP with healing of forefoot ulcers or amputations is evident in early studies even with the relatively few patients in those studies. More recent studies have largely been unable to replicate this association, quite possibly due to MAC, as most studies were conducted using patients with diabetes. Two studies have associated low AP with increased mortality.

2.5.6 Toe Pressure

Conrad and Green measured systolic TP when they investigated haemodynamic characteristics of the peripheral circulation.[224] TP was found to be equal to brachial pressure in healthy subjects and to be very low, 15.7 mmHg on

Table 15. Ankle pressure; all-cause and CV mortality.

Author year	Study (n)	Reference	Group, (n)	All-cause mortality (95% CI)	CV mortality (95% CI)	Follow-up
Bradbury 2010	BASIL trial, CLI patients (452)	AP ≥ 50 mmHg and no tissue loss	AP < 50 mmHg, (137)	HR 2.6 (1.3-5.0)	-	2 years
			AP ≥ 50 mmHg with tissue loss (222)	n.s.	-	
Sartipy 2018	Population of 60-90 year-olds (4940)	ABI < 0.9 and AP > 70 mmHg	AP ≤ 70 mmHg, (65)	HR 2.3 (1.8-3.1)*	HR 3.5 (2.3-5.2)*	10 years

* Only adjusted for age.

average, in patients that had toe amputation for ischaemic tissue loss.[225] Carter later reported a linear relationship between TP and clinical severity of lower limb PAD.[226] TP has acceptable diagnostic accuracy in indicating PAD in both diabetic and non-diabetic patients.[227] An inconsistency of low TP has been shown nonetheless, and the reliability of single low TP measurements has been questioned,[228] whereby the variability of TP has been estimated to be twice that of ABI.[229] Nevertheless, TP accurately identified 60% of CLTI patients in the IN.PACT DEEP trial, whereas AP met CLTI criteria in only 16% of cases.[182]

TP is a sensitive marker for healing of foot ulcers in both diabetic and non-diabetic patients.[230] Although prevalent MAC in the diabetic population can make ABI and AP less useful as markers, the digital arteries are infrequently affected.[183] In a study of over 1000 foot radiographs in a predominantly diabetic population (93% of those with diagnosed diabetes, and 100% with impaired glucose tolerance), observable MAC of the first dorsal metatarsal artery was found in only 1.4% of patients.[231] TP is thus often regarded as an alternative to AP or ABI in the presence of MAC or distal arterial disease at the level of the forefoot, and TP > 30 mmHg is regarded as indicating good healing potential.[232,233] Tay et al. reported good sensitivity (0.86) but mediocre specificity (0.58) for the healing of diabetic foot ulcers with TP > 30 mmHg.[234] A systematic review identified TP ≥ 45 mmHg as a marker for adequate perfusion to the foot, associated with a higher probability of healing of diabetic ulcers.[223]

TP has been proven useful in predicting the healing of digital or forefoot amputations. In a number of small studies with varying proportions of diabetic patients, TP threshold pressures for healing of forefoot amputations varied from 20,[235] 30[236] and 35 mmHg.[237] Holstein reported a healing of forefoot and digital amputations in 134 patients occurring in 17%, 59% and 78% of patients with TP < 20 mmHg, 20–29 mmHg and ≥ 30 mm Hg, respectively.[217] In a study of 333 patients undergoing toe, forefoot or midfoot amputations, TP ≥ 47 mmHg was associated with wound healing three times as likely compared to < 47 mmHg after adjusting for confounders, whereas ABI, TBI or ankle artery pulse velocities or waveforms were not related to healing.[238]

An association between low TP and increasing need for revascularisation has been reported in a small study of 49 Fontaine III–IV patients, in which the likelihood ratio for CLTI requiring invasive revascularisation within 6 weeks was found to be 7.0 in patients with TP < 30 mmHg and 0.15 with TP ≥ 50 mmHg.[239]

In a prospective study of 2511 diabetics with neuroischaemic foot ulcers, TP < 30 mmHg increased the unadjusted odds of of major amputation 1.7-fold.[222] In comparison, a study of 142 conservatively treated patients with chronic wounds and TP ≤ 50 mmHg found no difference in major amputations between subjects with TP < 30 mmHg and TP 30–50 mmHg.[240] Salaun et al. nonetheless, showed in the

COPART cohort of 212 CLTI patients with TP measurements that TP < 30 mmHg was associated with three-fold odds of amputation, compared to TP > 50 mmHg, and two-fold odds of amputation compared to TP 30–50 mmHg. The same study reported 1-year amputation rates for TP < 30 mmHg, 30–50 mmHg and > 50 mmHg to be 36%, 13% and 14%, respectively. The TP threshold for best sensitivity and specificity in predicting amputation was 29 mmHg.[63] As far as extremely low TP is concerned, limb loss at 3 years occurred in 60% of those with TP ≤ 10 mmHg, compared to 18% in those with TP 31–50 mmHg, in a study of 443 CLTI patients. A notable 46% of patients with TP ≤ 10 mmHg were amputated within one year with a three-year AFS of 8%.[241] A study of 95 revascularised patients with TP < 30 mmHg reported freedom from amputation after 5 years of follow-up differed significantly between groups with preoperative TP < 10 mmHg, 10–19 mmHg and 20–29 mmHg.[242]

Values of TP < 50 mmHg have been associated with a nearly four-fold risk of recurrent adverse cardiac events in type 2 diabetic patients with previous acute coronary syndrome.[243] Although it could be assumed that low TP would be associated with higher mortality, there are few published studies designed to assess this, rather than limb-related outcomes (Table 16). Fagher et al. were unable to demonstrate an association of either TP or ABI with 1-year mortality in type 2 diabetic patients with foot ulcers.[244] However, a study by Vallabhaneni et al. showed that very low TP (0–10 mmHg) in 252 CLTI patients was independently associated with 2-year mortality with an adjusted HR of 2.0, compared to TP 31–50 mmHg. The hazard was not significantly increased in patients with TP 11–30 mmHg. Furthermore, estimated 3-year survival with TP 0–10 mmHg, 11–30 mmHg and 31–50 mmHg were 53%, 41% and 34%, respectively.[241]

Andersen et al. studied 53 conservatively treated patients with 76 limbs with TP < 30 mmHg. They reported a 68% amputation rate and 60% mortality in patients with rest pain or gangrene after up to 65 months follow-up. In patients with claudication or no symptoms at all, amputation occurred in 16% and death in 10%. It is worth noting, that a significantly greater proportion of patients that manifested CLTI and amputees had TP < 10 mmHg.[245] The same authors also followed 95 patients with 122 limbs with TP < 30 mmHg, who had been revascularised. They found the estimated survival for all patients at 5 years was 80%, and freedom from amputation was 89%.[242] Bowers et al. followed 56 men with stable claudication and TP ≤ 40 mmHg. They used a composite end point of rest pain, tissue loss or gangrene, and reported an estimated freedom from events at one and three years to be 0.91 and 0.69, respectively. Taking mortality into account in the same study, event-free survival at one and three years was 0.85 and 0.59, respectively. For 56 control patients with stable claudication and TP > 40 mmHg, event-free survival at one and three years was significantly better at 0.98 and 0.89, respectively.[228]

Table 16. Toe pressure; all-cause mortality.

Author year	Study, population	Reference	Group, (n)	All-cause mortality (95% CI)	Follow-up
Fagher 2018	Type 2 diabetics with foot ulcers (236)	TP ≥ 30 mmHg	TP < 30 mmHg, (n/a)	n.s.	1 year
Vallabhaneni 2016	CLI patients (252)	TP 31-50 mmHg	TP 11-30 mmHg, (71)	n.s.	2 years (mean)
			TP 0-10 mmHg, (75)	HR 2.0 (1.3-3.1)	

As TP is largely unaffected by MAC, it appears to be reliable in a greater proportion of PAD patients than ABI. On the other hand, TP measurements may be more prone to variability than ABI. TP is apparently highly useful in predicting tissue viability in the forefoot, both in the context of wound healing and the risk of amputation. Therefore, the clinical value of TP in determining the need for revascularisation appears justified. As for general outcome, only one previous study on CLTI patients has associated very low TP with increased mortality.

2.5.7 Toe-Brachial Index

Carter determined TP for healthy subjects, for patients with IC and for patients with rest pain or tissue loss. He found a linear correlation of both TP and also TP as a percentage of brachial pressure, with the clinical severity of PAD. This correlation was evident in both diabetic and non-diabetic patients. Although there was significant overlap between groups for TP per se, TP expressed as a percentage of brachial pressure greatly reduced this overlap.[226] Although TBI is still sometimes considered superior to ABI for diagnosing PAD, a systematic review of seven publications found there was wide variation in both sensitivity (45–100%) and specificity (16–100%) when the presence or absence of PAD was confirmed with vascular imaging.[246] There are also studies that show no benefit for TBI over ABI for detecting PAD in diabetics.[247]

In patients with diabetes, TBI ≤ 0.7 has been associated with CV risk factors such as increased central arterial stiffness, increased intima-medial thickness, carotid plaque and low glomerular filtration rate.[248] In type 2 diabetic patients, high levels of high-sensitivity C-reactive protein and fibrinogen as markers of inflammation, pregnancy-associated plasma protein-A as a marker for acute coronary syndrome and increased carotid intima-medial thickness, have been associated with low TBI.[249,250] TBI < 0.6 was associated with a nearly three-fold risk of recurrent adverse cardiac events in patients with type 2 diabetes and previous acute coronary syndrome.[243]

Paaske and Tonnesen followed 43 CLTI patients for 2 years and measured TBI of both legs. Amputation was performed in 82% of patients with worst-leg TBI < 0.07, compared to 60% in those with TBI > 0.07.[251] One study reported a non-adjusted association of TBI < 0.70 with increased OR (19.2 [95% CI 2.4–156.0]) of a combined end point of ulcers and amputation in a mixed elderly population of 261 vascular surgery outpatients.[252] A post-endovascular revascularisation increase in TBI of ≥ 0.21, but not ABI, independently reduced the HR of MALE to 0.27 (95% CI 0.09–0.77), in a population of 218 CLTI patients with tissue loss. In the same study, TBI increase also predicted wound healing (HR 1.63, 95% CI 1.02–2.59).[253]

There are a handful of studies regarding TBI and mortality (Table 17). In the small series of 43 CLTI patients by Paaske and Tonnesen mentioned above, no significant differences in mortality with respect to TBI were found.[251] The population-based Hoorn study of 624 patients was conducted with follow-up for over 17 years. The authors reported that TBI < 0.7 was more prevalent in non-survivors, but it did not independently predict either CV or all-cause mortality.[172] However, in a mixed diabetic and non-diabetic cohort of 469 patients with a median follow-up of 7 years, age-and-sex adjusted TBI was inversely linearly associated with CV mortality in both diabetic and non-diabetic patients. The reference TBI was between 0.62 and 1.08. Fully adjusted HR of CV mortality for TBI < 0.40 was 2.3. For TBI 0.40–0.61, only age and sex adjusted HR increased but the difference did not remain significant after full adjustment.[211] In a prospective cohort study of 200 diabetic patients with microalbuminuria, TBI < 0.64 increased the adjusted HR of all-cause mortality by 3.2.[174] In the outpatient study by Suominen et al., for patients with ABI ≥ 1.3, TBI < 0.60 was independently associated with both overall (OR 2.21) and CV mortality (OR 4.9).[186]

A systematic review by Trevethan found variability of TBI to be greater than that of TP, especially in diabetic patients, and this variation was chiefly related to variations in brachial pressure. The author recommended multiple TBI-measurements on multiple occasions to overcome this variability.[254] The diagnostic sensitivity of TBI in detecting PAD may be better than that of ABI, but even it appears to be lower in diabetic than in non-diabetic patients.[255] Furthermore, the range of normal TBI is poorly defined.[256–258] Inter and intra-rater reliability of TP measurements using photopletysmography in diabetics has been found to be excellent, but that of brachial pressure poor or fair to good at the most. This limitation would inevitably negatively affect the

Table 17. Toe-brachial index; all-cause and CV mortality.

Author year	Study (n)	Reference	Group, (n)	All-cause mortality (95% CI)	CV mortality (95% CI)	Follow-up
Suominen 2010	PAD outpatients with ABI ≥ 1.3 (185)	ABI ≥ 1.3 and TBI ≥ 0.60	ABI ≥ 1.3 and TBI < 0.60, (112)	OR 2.21 (1.01-4.85)	OR 4.9 (1.5-16.0)	3.3 years (average
Hanssen 2012	Hoorn study (624)	TBI ≥ 0.7	TBI < 0.7, (160)	n.s.	n.s.	17.2 years (median
			TBI < 0.40, (102)	-	HR 2.3 (1.5-3.4)	
Hyun 2014	PAD outpatients (469)	TBI 0.62-1.08	TBI 0.40-0.61, (157)	-	n.s.	7 years (median)
			TBI > 1.08, (14)	-	n.s.	
Zobel 2014)	Diabetic patients (200)	TBI ≥ 0.64	TBI < 0.64, (30)	HR 3.2 (1.2-8.5)	-	6.1 years (median)

reliability of TBI.[259] However, in another study that utilised laser doppler flowmetry there was substantial diagnostic agreement, and especially for diabetic patients.[260]

Brooks et al. have proposed that TBI offers an advantage in assessing lower limb arterial blood supply only in patients with ABI ≥ 1.3.[261] Although TBI may be relatively unaffected by MAC, in the outpatients studied by Suominen et al., 28% of patients with ABI ≤ 0.9 had a TBI ≥ 0.6. This may very well reflect limitations in reliability regarding either or both pressure measurements, coupled with the incompletely defined threshold of normal TBI as well. The same rationale may, to some degree, explain the fact that 27% of patients in the same study with normal ABI had TBI < 0.6, even though MAC may have influenced this too.[186]

In a manner similar to TP, TBI overcomes some of the inherent limitations associated with MAC but, as with ABI, TBI suffers from the variability of brachial pressure measurements. A normal range for TBI has not yet been defined. These unachieved goals are reflected in conflicting results regarding TBI and outcome.

3 Aims

This thesis aims to clarify the role of angiographic imaging and pressure measurements of the lower limbs in predicting outcome for patients with symptomatic PAD, specifically:

1. To assess the effect of the extent and anatomical location of lower extremity atherosclerotic lesions on cardiovascular and overall mortality
2. To determine the association between Crural index and outcome
3. To determine the association between systolic toe pressure and outcome
4. To assess the impact of bilaterally low systolic toe pressure on the outcome

4 Materials and Methods

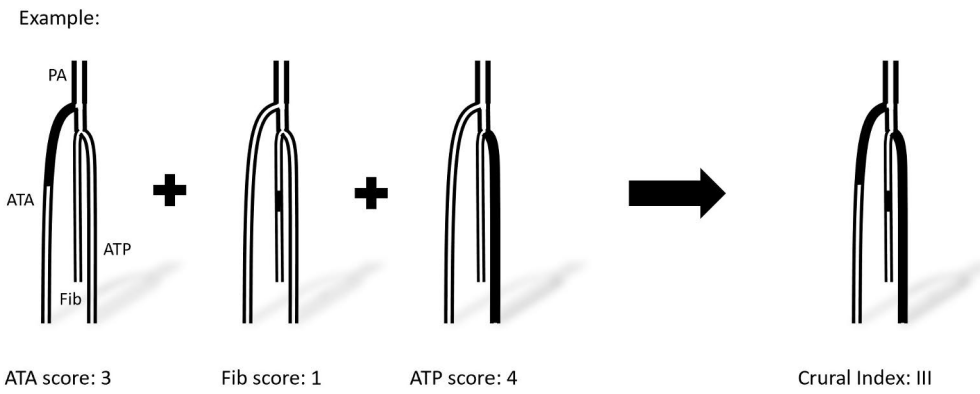
A total of 887 consecutive patients were admitted to the department of vascular surgery at Turku University Hospital, Finland for diagnostic or therapeutic DSA due to symptomatic lower extremity peripheral artery disease (Rutherford category 2–6) between January 2009 and August 2011. The patients were subsequently retrospectively reviewed after data were collected from hospital electronic databases and Statistics Finland. The study was approved by the Hospital District of South-Western Finland Ethics Committee. Patient consent was not required as the study was retrospective.

4.1 Patient Cohort and Study Designs

All invasive angiographies were ordered by a vascular surgeon. Patients were included in the study irrespective of urgency, or history of previous or subsequent examinations or treatments for PAD. The date of the first DSA was defined as the index date for follow-up. Dates and causes of death of study patients were collected from Statistics Finland and amputations data were collected from electronic patient files. A registering delay of 2 weeks for deaths in the electronic patient registry and up to 2 years for causes of death in Statistics Finland's database was taken into account in the timing of analysis of results.

Baseline variables that were collected from electronic patient files at or immediately prior to the index date included: sex, age, smoking status at the index date, serum creatinine and Rutherford classification for clinical severity of ischaemia. Medication data included statins, aspirin, clopidogrel, warfarin and novel anticoagulants. The following International Classification of Diseases coded diagnoses were recorded: CAD, cerebrovascular disease, hypertension, diabetes, sleep apnoea, chronic obstructive pulmonary disease (COPD), ESRD and dyslipidaemia. Modes of revascularisation (open surgical, endovascular and hybrid) subsequent to DSA were registered. A reliable medication history was unavailable for some patients, as they entered the study before the implementation of an electronic drug chart. Medication status was deemed unreliable for 7% (n=51) of the patients in study III.

All DSA images of the 887 patients were reviewed by a single investigator, who analysed the severity and extent of atherosclerotic lesions for aorto-iliac, femoropopliteal and infra-popliteal arteries separately as defined in the TASC II classification. In studies I and II, lesions in the aorto-iliac and femoropopliteal arteries were graded according to the TASC II classification into 5 categories: No significant stenosis: 0; TASC II A: 1; TASC II B: 2; TASC II C: 3; TASC II D: 4. All 3 major arteries of the shank i.e. the anterior and posterior tibial arteries and the peroneal artery, were graded separately according to the length of the total occlusion as follows: no occlusion: 0; < 5 cm: 1; 5 – < 10 cm: 2; 10 - < 15 cm: 3; ≥ 15 cm: 4. The sum of individual grades was then pooled into 5 grades, named the Crural Index (CIx), as follows: 0: 0; 1–3: CIx I; 4–6: CIx II; 7–9: CIx III; 10–12: CIx IV (Figure 8). According to the segment with the highest grade of arterial lesions, subjects were further categorised into three groups: predominant aorto-iliac, femoropopliteal or infrapopliteal. When segments had identical scores, the more proximal segment was used for categorisation. Additionally, arterial segments were classified on a binary 'yes or no' basis for any significant atherosclerotic lesions.



Scoring of individual crural arteries by total occlusion length	
None	0
Occlusion < 5 cm	1
5 cm ≤ occlusion < 10 cm	2
10 cm ≤ occlusion < 15 cm	3
Occlusion ≥ 15 cm	4

Total score	Crural Index
0	0
1-3	I
4-6	II
7-9	III
10-12	IV

ATA: anterior tibial artery;
ATP: posterior tibial artery;
Fib: fibular/peroneal artery;
PA: popliteal artery

Figure 8. Crural Index. Wickström 2022.

Standardised peripheral pressure measurements were obtained as part of the diagnostic work-up prior to the index DSA by technicians at the Department of

Clinical Physiology, Turku University Hospital, using a Nicolet VasoGuard (Nicolet Vascular Inc. Madison, WI, USA) photopletysmography device. Toes were preheated, measurements obtained with the patients supine and rested. Brachial, ankle and digital cuffs were inflated until disappearance of the photopletysmograph signal or up to > 250 mmHg and gradually deflated until reappearance of pulsatile signals. TP of the big toes were measured whenever possible. When this was not possible TP of the nearest available toe was measured. The means of 3–5 measurements of brachial pressure, AP and TP were recorded and used in the analysis. ABI and TBI were calculated from these mean values. AP, ABI, TP or TBI of at least one extremity was available for 732 patients. TP and TBI of at least one lower extremity were available for 727 patients. However, 28 patients had extensive tissue loss of the foot or had undergone previous amputation. Bilateral TP and TBI were thus available for 699 patients. Pressure indices for one patient were unavailable due to bilaterally incompressible brachial arteries. Standardised pressure measurements were not available for patients presenting urgently, as the service was not provided outside office hours.

The patient cohort in study III consisted of 732 patients. Systolic pressures for only the clinically relevant, symptomatic lower extremity were registered. When both limbs were symptomatic, pressures of the limb with the lowest TP were registered. When TP was not available, pressures for the extremity with the lowest AP were registered. TP was unavailable for 15 patients due to tissue loss or previous forefoot amputation and AP was unavailable for 12 patients due to pain, tissue loss or failure to co-operate.

The patient cohort in study IV consisted of 727 patients. The extremity with the lowest TP or having undergone previous amputation was defined as the ipsilateral lower extremity, regardless of clinical grade or symptoms of ischaemia. The other extremity was defined as the contralateral lower extremity.

Peripheral pressure measurements in studies III and IV were collected and pooled into categories for analysis according to the TASC II recommendation and the previously described association of ABI with CV events. AP data were pooled into four categories: < 50 mmHg, 50–69 mmHg, 70–250 mmHg (reference) and > 250 mmHg; ABI into six categories: < 0.25, 0.25–0.49, 0.50–0.74, 0.75–0.89, 0.90–1.30 (reference) and > 1.30; TP into three categories: < 30 mmHg, 30–49 mmHg and ≥ 50 mmHg (reference); TBI into three categories: < 0.25, 0.25–0.50 and ≥ 0.50 (reference).

4.2 Outcome Measures

Overall mortality was defined as death for any reason. CV mortality was defined as any cause of death coded according to the International Classification of Diseases

between I00–I42.5 or I42.7–I99 inclusive. AFS was defined as being alive without amputation above the ankle.

4.3 Statistical Analyses

IBM SPSS v. 22 (I-III) and v. 25 (IV) (IBM, Armonk, NY, USA) with R-statistics extension (IV) were used for analyses. Baseline categorical variables between groups were presented as percentages and continuous variables as mean +\- SD. Categorical variables were compared using Pearson's chi-square test. Normality of distribution for continuous variables were tested using the Shapiro-Wilk test and, since they were normally distributed within each group, compared with analysis of variance. Survival for each group and outcome were assessed by Kaplan-Meier survival analysis and survival between groups was compared by using the log rank test (I, II) and Wilcoxon sign rank test (III, IV). For each end point, baseline variables were first tested for an association with survival by univariate Cox regression. All variables with $P < 0.2$ (I, II, IV) or 0.15 (III) were included in multivariable Cox regression analysis for each outcome. In studies III and IV, p-values were Bonferroni-adjusted to further lower the risk of false positive observations. $P < 0.05$ were considered statistically significant. The C-index for each multivariable model of 60-month CV and overall mortality was determined to assess predictive power (IV).

5 Results

Study I assessed the association of CIx and the distribution of atherosclerotic lesions with mid-term overall mortality at 36 months in 887 patients. Study II assessed the association of CIx with long-term overall and CV mortality in the same patient cohort at up to 7 years follow-up. The mean age of patients entering Studies I and II was 72.4 years and ranged from 40–98 years. 57% of patients were male and 43% female. At 36 months follow-up, 295 (33%) patients had died and at up to 7 years follow-up, 408 patients (46%) had died, with 246 cases (60% of all deaths) of CV causes.

Study III assessed the association of ankle pressure, ABI, TP and TBI with overall and CV mortality and AFS at 36 months in 732 patients. The mean age of patients was 72 (SD 11) years. In this patient cohort, 58% were male and 42% female. There were no significant differences in baseline demographic factors between patient groups by TP categories, with the exception of age ($p < 0.001$) and the prevalence of statin use ($p = 0.021$). An increase in age and a decrease in the the prevalence of statin use was observed with decreasing TP.

Study IV examined the association of TP and TBI of both lower extremities with long-term overall and CV mortality of 727 patients at 60 months. Median follow-up time for the whole study cohort was 55.5 months and 67.0 months for survivors. At 7 years follow-up, 347 patients (48%) had died of which 210 (61%) of CV causes. A comparison of demographic factors between patient groups by contralateral systolic toe pressure categories (CL_TP) was conducted. The data showed that the prevalence of diabetes ($p = 0.011$) and a positive history of smoking ($p = 0.03$) differed significantly between groups, with diabetes and a negative smoking history more prevalent with decreasing CL_TP. Of all the patients, 17.7% were treated conservatively. The proportions of patients in the whole study cohort that had undergone at least one open surgical, endovascular or hybrid revascularisation during follow-up were 37.4%, 59.7% and 14.0%, respectively. Conservative treatment was significantly more common with decreasing TP ($p = 0.003$).

5.1 Crural Index, Lesion Distribution and Outcome

5.1.1 Study I

In Study I, comparison of the most severely diseased arterial segment showed a significantly shorter estimated overall survival (OS) for those with predominant crural disease (23.8 months, SE 0.8), as compared to those with predominant aorto-iliac (33.7 months, SE 0.7) or femoropopliteal disease (31.9 months, SE 0.5). A comparison of OS between groups by arterial segments with any significant atherosclerotic lesions revealed that OS was significantly worse in patients with isolated crural disease (26.6 months, SE 1.2), compared to those with isolated aorto-iliac (36.2 months, SE 0.5) or with isolated femoropopliteal (32.8 months, SE 1.3) disease. This was also the case when patients with isolated crural disease were compared to those with combined aorto-iliac and femoropopliteal disease and with combined aortoiliac and crural disease (33.3 months, SE 1.4 for both categories).

A comparison of patients across different severity categories within the same anatomical location revealed that OS for aortoiliac categories 1 ($p = 0.015$) and 2 ($p = 0.024$) was significantly higher than for category 3. There were no significant differences in OS between categories within the femoropopliteal segment. Mean estimated OS with CIx IV was 23.2 months (SE 1.1), which was significantly shorter than in all lower CIx categories ($p < 0.001$). OS for CIx III was also significantly shorter than for CIx I ($p = 0.044$) and CIx II ($p = 0.004$). When 3-year mortality was the outcome, the adjusted HR was more than doubled for CIx IV compared to CIx 0 (Table 18), and predominant crural disease increased the hazard 2.5-fold compared to predominant aorto-iliac disease (HR 2.5 [95% CI 1.5–4.0]).

Table 18. Crural index (Cix); all-cause mortality.

Cix (n)	Hazard ratio (95% CI)
CiX 0 (126)	Reference
CiX I (70)	1.04 (0.5-2.1)
Cix II (235)	1.1 (0.6-2.1)
Cix III (289)	1.4 (0.8-2.2)
Cix IV (167)	2.2 (1.3-3.7)

*p = 0.003

5.1.2 Study II

In Study II, survival analysis according to the most severely affected arterial segment had a significantly shorter mean estimated freedom from cardiovascular death (FCD)

and OS for patients with predominant crural disease, compared to those with predominant aorto-iliac or femoropopliteal disease ($p < 0.001$) (Figure 9). When comparing patients with predominant femoropopliteal disease with those with predominant aorto-iliac disease, both FCD ($p = 0.046$) and OS ($p = 0.015$) were significantly shorter. Multivariable analysis was carried out separately for ABI and TBI as confounding factors, due to their strong and similar associations with outcome. A multivariable model adjusted for TBI but not ABI, revealed predominant crural disease increased the HRs of CV death to 2.3 (95% CI 1.5–3.7) and of death for any reason to 2.2 (95% CI 1.5–3.1), when compared to those with predominant aorto-iliac disease. In a model adjusted for ABI but not TBI, HRs were higher at 2.6 and 2.5, respectively.

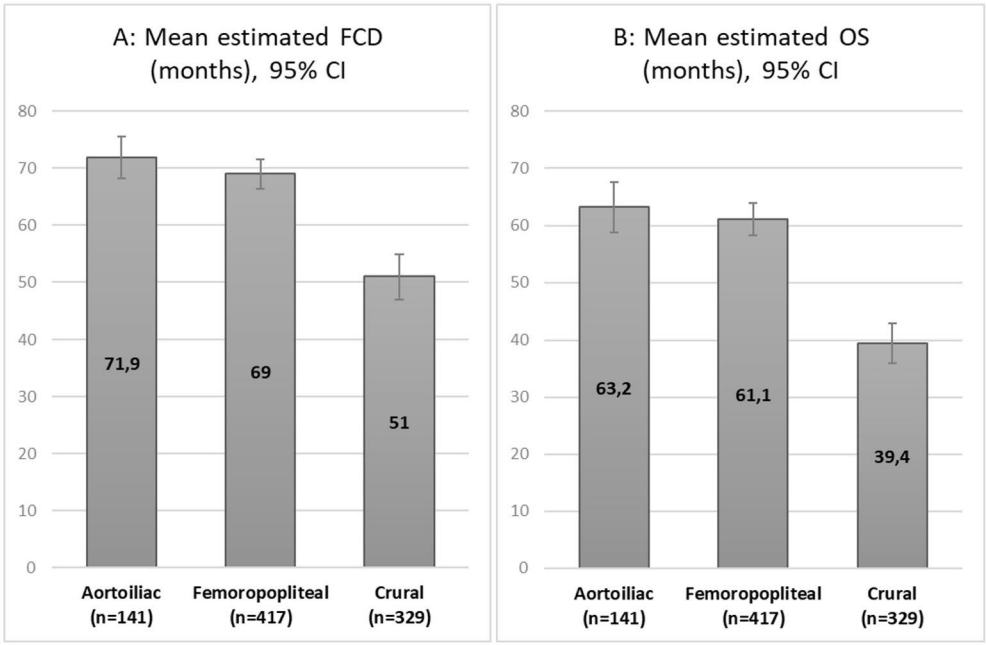


Figure 9. Most severely affected arterial segment; mean estimated (A) freedom from cardiovascular death (FCD) and (B) overall survival (OS).

Mean estimated FCD was significantly shorter in patients with CIx IV compared to those with CIx 0, I, II ($p < 0.001$) and III ($p = 0.003$). Even patients with CIx III had a significant disadvantage in FCD compared to those with lower CIx ($p < 0.001$). OS in patients with CIx IV was significantly reduced compared to all lower CIx categories ($p < 0.001$) and, in patients with CIx III, significantly shorter compared to those with CIx 0 ($p < 0.001$) and II ($p < 0.001$) (Figure 10). Multivariable analysis for CIx was also modelled for ABI and TBI separately. Other factors that warranted

adjustment were age, CAD, hypertension, diabetes, renal insufficiency, hyperlipidaemia and smoking history. In addition, COPD was added to the CV mortality model, and cerebrovascular disease was added to the all-cause mortality model. When TBI was included in the analysis as an independent variable, the HR of CV death in patients with CIx IV, compared to CIx 0, was 3.5, and of death for any reason, 2.5. The hazard of CV death was also increased in patients with CIx III (HR 2.2). With ABI as a confounding factor, the HR of CV death was similarly higher in patients with CIx IV, compared to CIx 0 (HR 4.6), as was the hazard of death for any reason (HR 3.3). The hazard of CV death and all-cause death in patients with CIx III was also significantly increased (HR 2.4 and 1.6, respectively), when compared to patients with CIx 0 (Table 19).

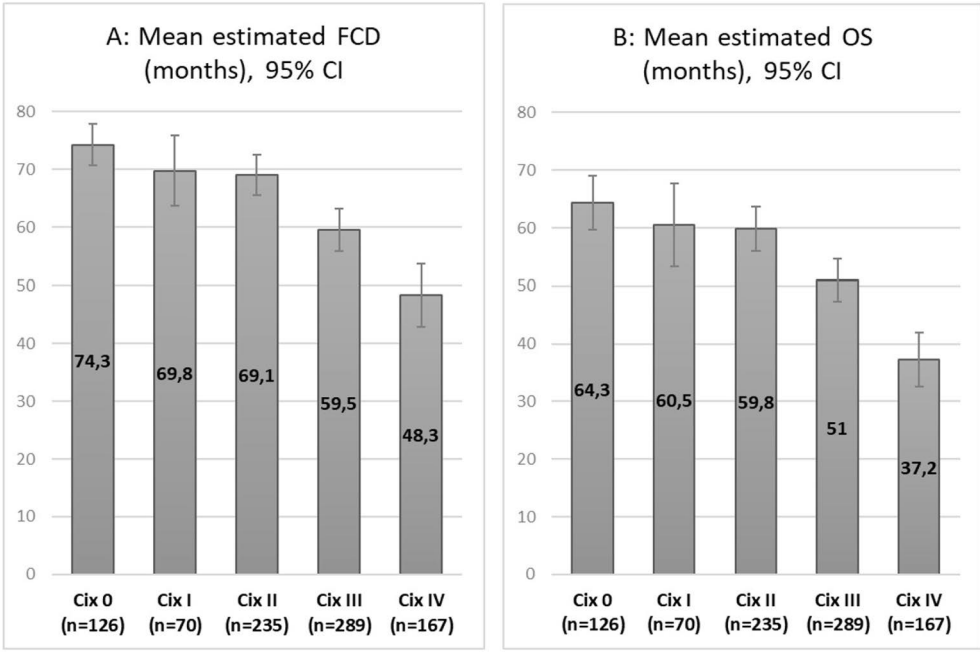


Figure 10. Crural Index (CIx); mean estimated (A) freedom from cardiovascular death (FCD) and (B) overall survival (OS).

Table 19. Crural Index (Cix); cardiovascular (CV) and all-cause mortality. Reference Cix 0. Model A: adjusted for TBI; model B: adjusted for ABI; p-values Bonferroni-adjusted.

A	All-cause mortality	
Cix	Hazard ratio (95% CI)	
Cix I	1.1 (0.7-1.9)	
Cix II	1.2 (0.8-1.7)	
Cix III	1.4 (1.0-2.1)	
Cix IV	2.5 (1.7-3.8)	p < 0.001*

B	All-cause mortality	
Cix	Hazard ratio (95% CI)	
Cix I	1.0 (0.6-1.7)	
Cix II	1.2 (0.8-1.7)	
Cix III	1.6 (1.1-2.3)	p = 0.024*
Cix IV	3.3 (2.2-4.9)	p < 0.001*

A	CV- mortality	
Cix	Hazard ratio (95% CI)	
Cix I	1.6 (0.8-3.4)	
Cix II	1.6 (0.9-2.9)	
Cix III	2.2 (1.2-3.8)	p = 0.007*
Cix IV	3.5 (1.9-6.4)	p < 0.001*

B	CV- mortality	
Cix	Hazard ratio (95% CI)	
Cix I	1.3 (0.6-2.8)	
Cix II	1.6 (0.9-2.8)	
Cix III	2.4 (1.4-4.2)	p = 0.002*
Cix IV	4.6 (2.5-8.2)	p < 0.001*

5.2 Peripheral Pressure Measurements and Outcome

5.2.1 Study III

Study III aimed to stratify patients with respect to FCD according to peripheral pressure categories (Figures 11 and 12). Mean estimated FCD in patients with TP < 30 mmHg was 29.4 months and significantly shorter than both 32.8 months in patients with TP 30–49 mmHg ($p = 0.001$) and 34.9 months in patients with TP ≥ 50 mmHg ($p < 0.001$). For AP, mean estimated FCD was the shortest for patients with AP < 50 mmHg (28.7 months) and AP > 250 mmHg (30.2 months). Patients with AP 70–250 mmHg had significantly longer FCD in comparison to patients with low AP ($p < 0.001$). Patients with TBI < 0.25 had significantly shorter mean estimated FCD (30.3 months) when compared to those with TBI 0.25–0.49 and to those with TBI ≥ 0.50 ($p < 0.001$). For ABI, patients with ABI < 0.25 and > 1.30 had the shortest FCD (27.5 and 29.3 months, respectively). FCD for ABI < 0.25 differed significantly from ABI categories 0.25–0.49 ($p = 0.007$), 0.50–0.74 ($p < 0.001$) and 0.75–0.89 ($p = 0.004$).

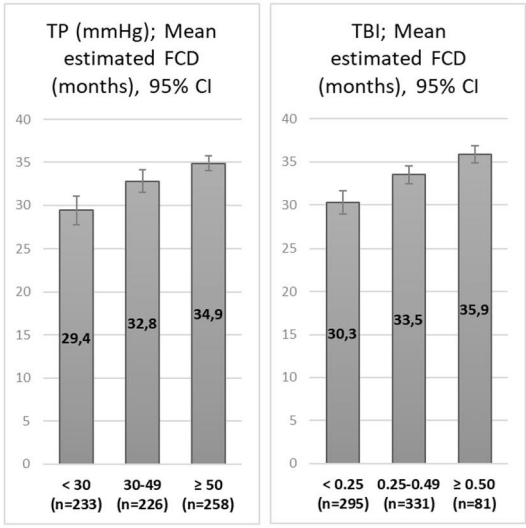


Figure 11. Toe pressure (TP) and toe-brachial index (TBI; mean estimated freedom from cardiovascular death (FCD).

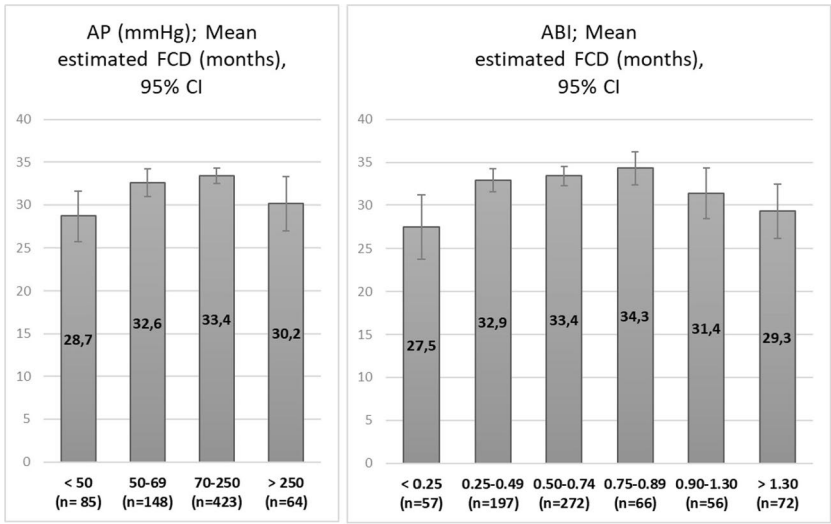


Figure 12. Ankle pressure (AP) and ankle-brachial index (ABI); mean estimated freedom from cardiovascular death (FCD).

Multivariable analysis was adjusted for age, CAD, CVD, hypertension, diabetes, ESRD, dyslipidaemia, COPD and smoking history. There was a significant hazard increase for CV mortality (HR 2.8) and all-cause mortality (HR 2.1) in patients with TP < 30 mmHg, compared to those with TP ≥ 50 mmHg (Table 20). A similar increase in hazard for the respective above-mentioned end points was observed in

patients with TBI < 0.25, when compared to patients with TBI ≥ 0.50 (HR 3.7 and 2.5, respectively). No significant hazard increase for either outcome was observed in the middle categories of TP or TBI, nor for any ABI category. Initially, AP > 250 mmHg was associated with an increased hazard of all-cause mortality, and AP < 50 mmHg was associated with CV mortality, but not after Bonferroni-adjustment.

Table 20. Toe pressure (TP) and toe-brachial index (TBI); all-cause and cardiovascular (CV) mortality.

All-cause mortality

TP (mmHg)	Hazard ratio (95% CI)	
< 30	2.1 (1.4-2.9)	p < 0.001*
30-49	1.3 (0.9-1.9)	

CV-mortality

TP (mmHg)	Hazard ratio (95% CI)	
< 30	2.8 (1.8-4.6)	p < 0.001*
30-49	1.6 (1.0-2.7)	

Reference: TP ≥ 50 mmHg

All-cause mortality

TBI	Hazard ratio (95% CI)	
< 0.25	2.5 (1.4-4.7)	p = 0.04*
0.25-0.49	1.9 (1.0-3.6)	

CV-mortality

TBI	Hazard ratio (95% CI)	
< 0.25	3.7 (1.5-9.2)	p = 0.05*
0.25-0.49	2.1 (0.8-5.4)	

Reference: TBI ≥ 0.50

Reference: TBI ≥ 0.50. p-values Bonferroni-adjusted.

5.2.2 Study IV

Study IV compared long-term all-cause and CV mortality at up to 60 months follow-up. Median follow-up time for the cohort was 55.5 months with survivors being followed-up for a median of 67.0 months. Nearly half, 347 (48%) patients had died at 7 years follow-up, and 210 (61%) of all deaths were due to CV causes.

Survival analysis revealed mean estimated FCD and OS at 60 months were lowest for patients with CL_TP < 30 mmHg (39% [SD 0.57] and 26% [SD 0.41], respectively) and ipsilateral systolic toe pressure (IP_TP) < 30 mmHg (56% [SD 0.60] and 41% [SD 0.45], respectively) (Figure 13). While FCD and OS differed significantly between all IP_TP categories (p < 0.001–0.003), only CL_TP ≥ 50 mmHg gave a significant survival advantage regarding both FCD and OS, when compared to lower CL_TP categories (p < 0.001).

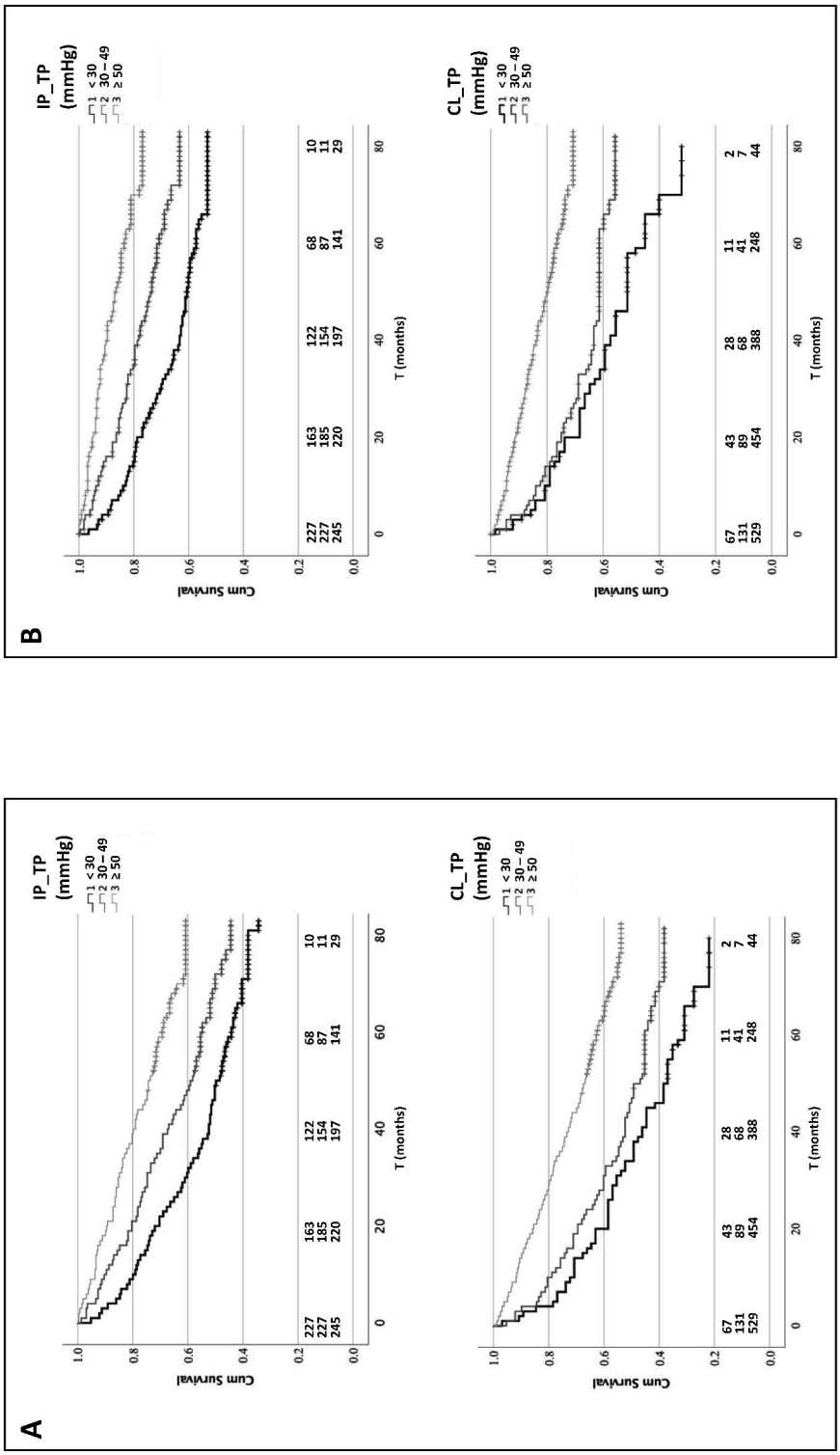


Figure 13. Ipsilateral (IP_TP) and contralateral (CL_TP) toe pressure; Kaplan-Meier survival curves for overall survival (A) and freedom from cardiovascular death (B).

In multivariable analysis adjusted for age, CAD, hypertension, diabetes, renal insufficiency, statin use and smoking history (Table 21), the HR of CV and all-cause mortality at 60 months was significantly higher in patients with IP_TP < 30 mmHg (2.9), compared to IP_TP ≥ 50 mmHg (2.2). Similarly, CL_TP < 30 mmHg (HR 2.8 and 2.4, respectively for CV and all-cause mortality) and 30–49 mmHg (HR 1.9 and 1.8, respectively) increased the hazard of both end points, compared to the reference CL_TP ≥ 50 mmHg. Adjusted hazard with IP_TP 30–49 mmHg no longer significantly differed from IP_TP ≥ 50 mmHg after Bonferroni adjustment. In ROC analysis, of all individual TP and TBI variables, only IP_TP showed acceptable C-index agreement with CV mortality as the outcome (0.702 [SD 0.021]).

Table 21. Ipsilateral and contralateral systolic toe pressure (STP) and toe-brachial index (TBI); all-cause and cardiovascular (CV) mortality.

Ipsilateral	All-cause mortality	
STP (mmHg) (n)	Hazard ratio (95% CI)	
< 30 (227)	2.2 (1.7-3.0)	p < 0.001*
30-49 (227)	1.5 (1.1-2.0)	p = 0.09

Ipsilateral	CV-mortality	
STP (mmHg)	Hazard ratio (95% CI)	
< 30	2.9 (2.0-4.1)	p < 0.001*
30-49	1.6 (1.1-2.4)	p = 0.13

Contralateral	All-cause mortality	
STP (mmHg) (n)	Hazard ratio (95% CI)	
< 30 (67)	2.4 (1.8-3.4)	p < 0.001*
30-49 (131)	1.8 (1.4-2.3)	p < 0.001*

Contralateral	CV-mortality	
STP (mmHg)	Hazard ratio (95% CI)	
< 30	2.8 (1.9-4.1)	p < 0.001*
30-49	1.9 (1.4-2.7)	p < 0.001*

Reference: STP ≥ 50 mmHg

Ipsilateral	All-cause mortality	
TBI (n)	Hazard ratio (95% CI)	
< 0.25 (267)	2.1 (1.5-2.9)	p < 0.001*
0.25-0.49 (348)	1.6 (1.3-2.1)	p < 0.001*

Ipsilateral	CV-mortality	
TBI	Hazard ratio (95% CI)	
< 0.25	3.3 (1.8-6.0)	p < 0.001*
0.25-0.49	2.0 (1.1-3.6)	p = 0.27

Contralateral	All-cause mortality	
TBI (n)	Hazard ratio (95% CI)	
< 0.25 (80)	2.1 (1.5-2.9)	
0.25-0.49 (279)	1.6 (1.3-2.1)	p < 0.001*

Contralateral	CV-mortality	
TBI	Hazard ratio (95% CI)	
< 0.25	2.5 (1.7-3.7)	p < 0.001*
0.25-0.49	1.5 (1.1-2.1)	p = 0.05*

Reference: TBI ≥ 50 mmHg. p-values Bonferroni-adjusted.

When comparing FCD and OS between patients with IP_TP < 30 mmHg grouped according to CL_TP, those with CL_TP ≥ 50 mmHg had a significant survival advantage (p = 0.005 and 0.002, respectively) compared to those with bilateral TP < 30 mmHg. Even among patients with IP_TP 30 – 49 mmHg, OS was significantly longer in patients with CL_TP ≥ 50 mmHg than in patients with CL_TP 30–49 mmHg (p = 0.014).

6 Discussion

The phenomenon that PAD predisposes patients to premature death and limb loss is well established in the literature. It is also evident that the increase in mortality is to a significant extent caused by CVD that results in MI, stroke or heart failure.[166] PAD should be considered an indicator for generalised atherosclerosis that warrants adequate lifestyle modifications and pharmacological therapy for CV risk reduction.[42] Modification of risk factors is especially important in patients at the highest risk of CV mortality and morbidity.[165] In a fairly recent British study on 28484 symptomatic PAD patients, only 22.6% were receiving recommended antiplatelet and statin therapy.[40] Patients with both PAD and CAD or cerebrovascular disease tend to receive better medical treatment than those with PAD alone.[262] Compliance with adequate secondary prevention reduces mortality.[263,264] There is some evidence that high-dose statin therapy and combined antithrombotic and anticoagulant therapy reduce both amputation rates and CV mortality in PAD-patients, but gains from aggressive pharmacotherapy come at the cost of increased adverse, potentially serious side-effects, such as myo- and hepatopathy, progression of diabetes, and major bleeding.[64,265–268] It has therefore become increasingly important to identify the patients who will benefit from aggressive medical treatment, but will also tolerate the possible side-effects.

The increase in risk of death and amputation appears to be proportional to the severity, location and extent of atherosclerotic disease as measured by clinical signs and symptoms, pressure measurements or arterial imaging. Yet risk stratification data for PAD patients is still lacking. The need for risk stratification is especially underlined for CLTI patients. This is necessary in order to: complement decision-making in vascular interventions, evaluate outcomes, improve the use of resources, and facilitate meaningful comparison of results and quality between trials, facilities and even individual physicians.[269] There is also an evident need for more effective risk stratification regarding amputations for patients with CLTI.[241] Previously suggested risk stratification schemes for CLTI have on occasion included angiographic status as part of a scoring system based on multiple variables.[110,270] The Society for Vascular Surgery wound, ischaemia, foot infection (WIfI) classification is an attempt to stratify the risk of amputation and benefit of revascularisation based

on the severity of: tissue loss, ischaemia and infection in the foot. For ischaemia, TP and $TcPO_2$ are interchangeable variables in the classification, and both directly correlate to AP in accordance with the TASC II recommendation. Correlating intervals for ABI are also stated (Table 22).[271] The WIfI has been associated with AFS in retrospective studies and meta-analyses. Its effect on estimating the benefits of revascularisation and ability to stratify risk remain to be proven, however.[272] The benefit of incorporating ABI into the Framingham risk score has been explored. For instance, although the net reclassification improvement was modest, ABI added to both the sensitivity and specificity of the score in predicting mortality and CVD events for the ARIC study population. The greatest benefit was found in patients with an intermediate score.[273] A pooled analysis of 20 studies, including the ARIC study, from the ABI Collaboration by Fowkes et al. came to a similar conclusion.[274]

Table 22. WIfI classification, grading of ischaemia.

Grade	ABI	AP (mmHg)	TP, TcPO2 (mmHg)
0	≥ 0.80	> 100	≥ 60
1	0.6-0.79	70-100	40-59
2	0.4-0.59	50-70	30-39
3	≤ 0.39	< 50	< 30

WIfI: Wound, Ischaemia, foot Infection; ABI: ankle-brachial index; AP: ankle pressure; TP: toe pressure; TcPO2: transcutaneous oxygen partial pressure. Adapted from: Mills et al. 2014.

6.1 Lesion Distribution, Extent and Outcome

Radiographically observable arterial calcification or atherosclerotic lesions at almost any site, even the breast arteries,[77] have been associated with an increased mortality. The majority of previous imaging studies show that mortality rises with increasing extensiveness of atherosclerotic lesions, even within one specific arterial bed. Results of principal disease location in the arteries of the leg predisposing patients to the highest risks are ambiguous. In contrast to our findings, a number of studies have found that a proximal distribution of PAD lesions results in greater mortality, compared to a more distal distribution.[75,76,104] The study by Aboyans et al. used angiography,[76] whereas Vogt et al. used segmental pressure measurements,[75] which may underestimate the presence of lesions distal to the most proximal significant lesion. Criqui et al. defined distal disease as lesions below the ankle.[104] There is a perceivable bias within the existing literature towards distal lesions resulting in the worst prognosis. Attempts have been made to quantify the extent of infrapopliteal lesions in a meaningful way, such that prognostic data could be extracted and used to stratify risk for life and limb. So far, no such classification system has been widely

adopted or validated for this purpose. The GLASS system certainly has potential to provide a lesion-anatomy oriented tool for making decisions and predictions concerning revascularisations in the future, but validating and adopting it for clinical use will take time.[14]

Results from studies I and II showed that the hazard of all-cause and CV mortality was greatest in patients with predominantly infrapopliteal PAD among symptomatic PAD patients undergoing angiography, and also in those patients with the most extensive crural lesions, as indicated by the Crural Index.

6.2 Pressure Measurements and Outcome

The ideal peripheral pressure measurement should be useful for diagnosing PAD, assess the degree of limb ischaemia, predict patient outcome, and measure the efficacy of interventions. The ability to predict tissue healing is important in decision-making regarding the level of amputation. Although ABI is important in the diagnosis of PAD, TP is more useful for assessing the viability of tissue of the foot.[275] Similarly, Ouriel and Zarins suggested, that whereas ABI is more useful in diagnosis than AP, the latter is the better predictor of limb viability.[131] A systematic review and meta-analysis considered the number of studies on TP and TBI to be insufficient for a reliable prognostic comparison to ABI to be made regarding the healing of diabetic foot ulcers and amputations. The authors of that review found ABI to perform poorly in predicting ulcer healing and only moderately for predicting amputation.[276] There is, however, overwhelming evidence to support the use of ABI in the diagnosis of PAD, and the evidence is robust enough to support the contention that abnormal ABI predicts both all-cause and CV mortality. ABI evidently provides prognostic information that cannot be derived from conventional risk factors alone.[42] Even so, ABI does have its well-known limitations, particularly those related to MAC that is present in a significant proportion of high-risk patients. This may at least partly explain some conflicting results in the attempts to show linearity in the increase of risk with the degree of abnormality of the ABI. The reliability of AP measurements is adversely affected by MAC as well. Both AP and ABI are relatively ineffective in detecting PAD for diabetics with foot ulcers.[277] There is conflicting evidence regarding the usefulness of AP in predicting amputation, and few studies have examined its relationship with mortality. Salaun et al. compared the ability of AP, TP and $TcPO_2$ to predict major amputation in CLTI patients by subjecting the data to ROC analysis. Of these potential indicators, AP was least useful, and TP was the best indicator (area under the curve 0.548 and 0.678, respectively).[63] Inconsistencies in the methods for determining ABI can also make it difficult to interpret and compare results. For example, the large population-based, and widely cited ARIC study used ABI but measured in only one leg, thus introducing a

noteworthy systemic flaw into the study.[278] The present study could not identify meaningful risk stratification for different values of ABI, with only extremely low or high ABI tending to associate with poor outcome. The results may have been different, had ABI categories been chosen differently, or had the lowest of the tibial artery pressures been used instead of the highest pressure.

TP and TBI may overcome some limitations of ABI, but these metrics have hitherto been used to either estimate tissue viability and healing potential, or as a secondary diagnostic investigation for PAD in patients with abnormally high ABI. TP has been shown to associate with the risk of amputation in some studies, but there are few studies that investigate the ability of TP to predict mortality, with only one study associating very low TP with increased mortality.[241] TBI has been associated with all-cause and CV mortality in a handful of studies. Similar to that found for TP, some use has been found for TBI in assessing limb viability and predicting amputation, especially in the diabetic population. Some authors advocate that TP should be used for evaluating all patients with diabetes or CLTI.[63,182,279] It has also been suggested, that TBI measurements should be included for all patients with suspected PAD, and not used exclusively for those with suspected MAC.[181] However, TP and TBI are not entirely without their own limitations. First, there is no real consensus regarding normal values of either TP or TBI.[280] Second, even though excellent big-toe pressure reproducibility has been reported by some authors,[281] TP may still be susceptible to more variation than AP.[229,282] For example, TP was reported to have an intra-rater error of +/- 26 mmHg and an inter-rater error of +/- 30 mmHg in one small study on diabetic patients.[283] The reliability of single low TP measurements has been questioned,[228] and instead the routine use of multiple TP measurements has been advocated.[284] Current objective criteria for CLTI include ABI < 0.4, AP < 50 mmHg and TP < 30 mmHg, but recent guidelines acknowledge the obvious limitations of pressure measurements and emphasise clinical presentation.[14]

Very few studies have undertaken a side-by-side comparison between ABI and TP or TBI for predicting mortality. Zobel et al. found rather similar predictive power for ABI and TBI as both continuous variables, and using a threshold of ABI < 0.9 or TBI < 0.64 for type 2 diabetics with microalbuminuria, after taking into account traditional risk factors. After complete adjustment, TBI independently predicted mortality but ABI did not.[174] Studies III and IV show that the risk of all-cause and CV mortality increases linearly with decreasing TP and TBI categories in symptomatic PAD patients, and thus they add to previously scarce evidence. Further, studies III and IV support the notion that more widespread, bilateral disease yields a comparatively poor prognosis, in that bilaterally low TP or TBI incrementally increases both all-cause and CV mortality, and may further aid in risk stratification.

6.3 Strengths, Limitations and Future Aspects

This study comprised a series of retrospective, single-centre studies of highly selected symptomatic PAD patients whom were undergoing clinically justified angiography at a university hospital. Therefore, this thesis is not generalisable to the general population, or even to vascular clinic outpatients as a whole. Furthermore, since the period of data collection between 2009 and 2011, a paradigm shift in the diagnostic and therapeutic process for lower limb ischaemia has occurred, with office-based DDUS allowing for a more reliable identification of patients with proximal lesions. For these patients, there is a now a preference for diagnostic CTA and therapeutic hybrid procedures, which abolish the need for primary diagnostic angiography. Given the continuing trend of increasingly using CTA or MRI for primary diagnostic imaging of PAD patients, abundant data are ever increasingly available for future studies on lesion distribution using these modalities. A major caveat regarding studies I and II is the fact that all angiographs were assessed solely by the principal investigator. A multi-observer setting would have significantly improved the validity of these two studies. Furthermore, validity of the comparison of different arterial segments is hampered by the use of different grading systems. The CIx was designed to quantify the crural arterial segments affected by atherosclerosis, as measured by total occlusion. The TASC II classification, on the other hand, is not only based on the extensiveness of lesions, but also on lesion location. That classification was originally designed to predict the degree of technical challenge and the expected patency of endovascular revascularisations.

The retrospective approach generates the problems of erroneous and incomplete data. The latter is exemplified by the information concerning medication was lacking in 7% of subjects in study III. However, its effect on choosing covariates for multivariable analysis in these studies is probably negligible. Even if the overall number of patients in the studies is acceptably large compared to many previous studies, the numbers of patients within some groups, such as low CL_TP, are low. Although there are apparent non-significant trends in outcome, particularly between groups with different peripheral pressures, observing any underlying significant associations would have warranted a larger study population.

The study includes a broad spectrum of PAD patients at different stages of treatment i.e. some with previous revascularisations or redo-revascularisations, and some with previous amputations. This may be regarded as a weakness, but the study population does accurately reflect a real-world clinical setting with symptomatic and thus high-risk PAD patients, where the risks to both life and limb are tangible. Whether or not TP accurately predicts outcome in all PAD outpatients, including those treated conservatively, would warrant another study. One might further speculate whether TP or TBI would outperform the robustly proven, yet inherently limited, predictive capability of ABI in a population-based setting.

When assessing therapeutic success in vascular surgery, technical end points such as freedom from target lesion revascularisation, and graft or vessel patency are frequently used. Similarly, for risk assessment, hard end points such as death, MACE or amputation, are favoured. The studies included in this thesis make no exception in this regard. From a humane and economical perspective however, it is vital that future research takes into consideration quality-of-life driven functional end points such as dependency, symptom relief, ambulatory and discharge status. A handful of studies reporting such long-term associations for findings in pre-procedure imaging[121] and ABI,[31,192] do indeed exist. In terms of risk-based clinical decision making, TP measurement and quantification of crural atherosclerotic lesions may provide simple tools to identify the patients with little to lose – and much to gain.

7 Conclusions

Findings of the presented studies on symptomatic PAD patients undergoing angiography may be summarised as follows:

1. A predominantly or exclusively infrapopliteal distribution of atherosclerotic lesions in the lower extremities and increasingly extensive lesions in the crural arteries are independently associated with increased cardiovascular and all-cause mortality.

2. A high Crural Index is independently associated with increased mortality.

3. Estimated cumulative survival and freedom from cardiovascular death can be stratified according to TP categories < 30 mmHg, 30–49 mmHg and ≥ 50 mmHg in the symptomatic lower extremity, with the lowest TP category independently associated with increased all-cause and cardiovascular mortality and decreased AFS.

4. Bilaterally low TP that reflects widely distributed atherosclerotic disease, is associated with significantly shorter OS and FCD, when compared to unilaterally low TP.

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