Published in final edited form as:

Circ Res. 2021 June 11; 128(12): 1818–1832. doi:10.1161/CIRCRESAHA.121.318535.

Epidemiology of Peripheral Artery Disease and Polyvascular Disease:

Aday – Epidemiology of PAD

Aaron W. Aday, MD, MSc[1], **Kunihiro Matsushita, MD, PhD**[2,3]

[1] –Vanderbilt Translational and Clinical Cardiovascular Research Center, Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, TN

[2] –Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[3] –Division of Cardiology, Johns Hopkins School of Medicine, Baltimore, MD

Abstract

Atherosclerotic lower-extremity peripheral artery disease (PAD) is increasingly recognized as an important cause of cardiovascular morbidity and mortality that affects more than 230 million people worldwide. Traditional cardiovascular risk factors, including advanced age, smoking, and diabetes, are strongly linked to an increase risk of PAD. Although PAD has been historically underappreciated compared to coronary artery disease and stroke, greater attention on PAD in recent years has led to important new epidemiologic insights in the areas of thrombosis, inflammation, dyslipidemia, and microvascular disease. In addition, the concept of polyvascular disease, or clinically-evident atherosclerosis in multiple arterial beds, is increasingly identified as a particularly malignant cardiovascular disease worthy of special clinical attention and further study. It is noteworthy that PAD may increase the risk of adverse outcomes in similar or even greater magnitude than coronary disease or stroke. In this review, we highlight important new advances in the epidemiology of PAD with a particular focus on polyvascular disease, emerging biomarkers, and differential risk pathways for PAD compared to other atherosclerotic diseases.

Keywords

peripheral artery disease; epidemiology; polyvascular disease; vascular disease

Subject terms:

peripheral vascular disease; risk factors; atherosclerosis

Correspondence to: Aaron W. Aday, MD, MSc, Division of Cardiovascular Medicine, Vanderbilt University Medical Center, 2525 West End Avenue Suite 300, Nashville, TN 37203, Phone: 615-875-8788, Fax: 615-322-3837, aaron.w.aday@vumc.org.

Introduction

Lower extremity peripheral artery disease (PAD) is characterized by stenosis or occlusion anywhere from the aortoiliac segment to the pedal arteries.[1] Many different disease processes can cause obstruction in these vessels, but the vast majority of cases are due to atherosclerosis, which will be the focus of this review. Although PAD has long been underappreciated compared to coronary artery disease (CAD) and cerebrovascular disease, PAD is increasingly recognized as an important cause of cardiovascular morbidity and mortality. Although many risks are shared between PAD and other forms of atherosclerosis, epidemiologic data have increasingly made it clear that PAD warrants recognition as a unique entity. In this review, we provide a summary of key epidemiologic insights into PAD with important updates since last reviewed in this journal.[2] We also discuss PAD in the context of polyvascular disease, an important conceptual framework that has furthered our understanding of atherosclerotic risk.

Defining PAD and Polyvascular Disease

The scope of this review is limited to PAD due to atherosclerosis and does not include nonatherosclerotic causes, such as Buerger's disease,[3] vasculitis,[4] and fibromuscular dysplasia.[5] PAD can affect any artery perfusing the lower extremities. The classic symptom of PAD is intermittent claudication (IC), characterized by cramping, pain, or fatigue in the lower extremities brought on by exertion and relieves by rest, typically within 10 minutes.[1] Symptoms may occur in the buttocks, thigh, or calf and often correspond to the proximal level of arterial obstruction. Although IC can be detected as part of a standard medical history, there are numerous validated claudication questionnaires used in a variety of epidemiologic studies.[6] Importantly, many patients with PAD do not experience typical IC and, instead, have atypical limb symptoms or no clear limb symptoms at all.[7] The notion of "asymptomatic" PAD should be carefully recognized, as patients with PAD, regardless of leg symptoms, have poorer prognosis and reduced limb function compared to those without. In addition, some patients may reduce their daily activity to palliate limb symptoms.[8]

Chronic limb-threatening ischemia (CLTI), also referred to as critical limb ischemia, is a severe form of PAD defined by ischemic rest pain, tissue loss, or gangrene.[1, 9] Symptoms should be present for a minimum of 2 weeks and be accompanied by objective limb hypoperfusion (see below). Rest pain typically involves the distal limb but may extend proximally in more severe cases, and it may worsen with elevation and improve with dependency. Acute limb ischemia (ALI) is another severe manifestation of PAD, defined by sudden, severe hypoperfusion of the limb over a period of <2 weeks.[1] Symptoms can include pain, pallor, pulselessness, poikilothermia, paresthesias, and paralysis with loss of sensation and motor function occurring in more severe cases. Although ALI may occur in the setting of PAD, it frequently occurs as a result of cardiac or artery-to-artery thromboembolism in the absence of significant peripheral atherosclerosis.

Since atherosclerosis is a systemic disease process, recent attention has focused on the coincidence of PAD with atherosclerosis in other arterial beds, most commonly CAD and cerebrovascular disease (occasionally including renal artery or mesenteric atherosclerosis).

This framework, termed polyvascular disease, is defined by the presence of atherosclerosis in ≥2 arterial beds.[10] Although definitions vary, qualifying atherosclerosis is typically either symptomatic or resulting in significant vessel stenosis (e.g. >50%).[11] Increasingly, polyvascular disease is being used to identify patients at heightened risk of cardiovascular and limb events who may benefit from intensive secondary preventive therapies. Indeed, the 2018 American Heart Association/American College of Cardiology (AHA/ACC) Cholesterol Guideline categorizes patients with two or more major atherosclerotic cardiovascular diseases as very high-risk.[12]

Diagnosis

Because the majority of patients with PAD lack typical leg symptoms, means of objectively diagnosing PAD are critical. In accordance with the 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity PAD, the resting ankle-brachial index (ABI) is considered the first-line test for diagnosing PAD.[1] In this test, a sphygmomanometer cuff and Doppler probe are used to calculate the systolic blood pressure in both brachial arteries as well as the bilateral dorsalis pedis and posterior tibial arteries with the patient in the supine position.[13] The ABI is the ratio of the higher reading of the two ankle pressures (dorsalis pedis and posterior tibial) over the higher reading of right or left brachial pressure and should be calculated in each limb. An ABI ≤ 0.90 in either limb is diagnostic of PAD.[1] The sensitivity and specificity of the resting ABI are generally reported as >80%.[14–16] However, these measures are primarily derived from studies of symptomatic PAD, and the performance of the ABI in individuals with atypical or absent limb symptoms is less understood. Nonetheless, given the robust association of ABI with mortality and morbidity, the AHA/ACC 2016 PAD Guideline acknowledges that the measurement of ABI is reasonable in persons at increased risk of PAD even when leg symptoms are absent.[1] In the setting of non-compressible, calcific ankle vessels, a toe-brachial index (the ratio of toe systolic blood pressure to brachial systolic blood pressure) with a threshold of ≤ 0.70 can be used to diagnose PAD. In cases of suspected PAD but normal resting ABI, post-exercise ABI measures may increase the yield of testing.[17]

Additional imaging modalities, while not required to diagnose PAD, may be useful in assessing disease distribution and planning for revascularization.[1] Duplex ultrasonography, computerized tomography angiography, and magnetic resonance angiography are all widely available and capable of detecting arterial stenosis throughout the limb. Invasive angiography is the gold standard for diagnosing lower limb stenotic lesions, although it is typically reserved for procedural planning or in cases where prior testing is inconclusive. Additional methods to assess limb perfusion include toe arterial waveform analysis, transcutaneous oxygen pressure, and skin perfusion pressure. Although a full discussion of these methods is outside the scope of this review, they may be particularly helpful in guiding management of patients with suspected CLTI.[18]

Prevalence, Incidence, and Temporal Trends

• Overall PAD

A recent systematic review estimates that the global prevalence of PAD was 5.6% in 2015, indicating that approximately 236 million adults were living with PAD worldwide.[19] The prevalence was higher in high-income countries than low- and middle-income countries (7.4% vs. 5.1%), but, reflecting the population size, most individuals with PAD (72.9%) were in low- and middle-income countries. Looking at this systematic review and the prior systematic review[20] from the same research group, the prevalence of PAD has increased from 2000 to 2015 by ~45% globally (~18% in high-income countries and ~58% in low- and middle-income countries) (Table 1).

The prevalence of PAD in the US is estimated to be ~7%, affecting 8.5 million adults.[21] However, we should note that this estimate is predominantly based on data collected in the 1990s. Notably, the National Health and Nutrition Examination Survey (NHANES) measured ABI only in its cycle of 1999–2004.[22] Given the recent changes in the prevalence of atherosclerotic risk factors (e.g., epidemics of diabetes[23] and declining prevalence of conventional cigarette use[24]), a more contemporary estimate of PAD prevalence is required. Another caveat is that data on the prevalence of PAD in individuals aged 80 years or older, the population most rapidly growing in the US,[25] are sparse.

• CLTI

Limited epidemiological data are available for CLTI. A study using data from MarketScan (database of millions of patients across the US from Medicare and Medicaid programs and large employers' health plans) estimated that the prevalence of CLTI was 1.3% among individuals aged 40 years or older in a given year between 2003 and 2008.[26] In this specific dataset, this accounted for 11% of overall PAD. The prevalence of CLTI seemed largely constant in those years. Similarly, a study using data from the Nationwide Inpatient Sample (NIS) demonstrated that the number of admissions related to CLTI was generally stable between 2003 and 2011.[27]

• Amputation

When we interpret statistics of non-traumatic lower extremity amputation in the context of PAD, we should keep in mind the two aspects of amputation: (1) an outcome of severe PAD and (2) an important therapeutic procedure to save a patient's life or limb. The decline in the rate of non-traumatic lower extremity amputation in the US has been reported from the 1990s to the beginning of the 2000s.[28, 29] However, a recent report using data from the NIS demonstrated a concerning increase in amputation rate after 2009 in persons with diabetes. Specifically, the age-adjusted rate of non-traumatic lower extremity amputation has increased by 50% from 2009 (3.1 per 1,000 adults) to 2015 (4.6 per 1,000 adults).[30] A similar increasing trend has been seen through 2018 among US veterans.[31] This increase in amputation rate is mainly due to an increase in minor amputations below the ankle, although a full explanation for this negative trend remains unknown.[29, 30] A recent review provides more details on the epidemiology of lower extremity amputations.[32]

Racial Disparities of PAD

Prior analyses have generally demonstrated a higher prevalence of PAD among Black individuals compared to non-Hispanic White individuals.[33–35] For instance, an analysis from 7 different community-based cohorts showed that both male and female Black individuals had the greatest prevalence of PAD, defined by an ABI <0.90, among all race groups.[36] Among men, Hispanic, American Indian, and non-Hispanic White individuals had similar prevalence rates, while individuals of Asian descent had the lowest prevalence. These trends were similar for women except for American Indian individuals, who had a prevalence similar to Black women with advancing age. Lifetimes estimates of PAD risk, defined by an ABI <0.90, suggest that 30% of Black individuals and 20% of non-Hispanic White individuals will develop PAD.[37] Data linking race to incident PAD are limited. For a more detailed discussion, see the review entitled “Racial Disparities in PAD” in this compendium.

Traditional Cardiovascular Risk Factors and PAD/Polyvascular Disease

Many traditional cardiovascular risk factors are shared between PAD, CAD, and other atherosclerotic diseases. However, several important findings in recent years have emphasized a differential pattern between some risk factors and atherosclerosis in different beds (Table 2). Although these findings have advanced our epidemiologic understanding of atherosclerotic disease, the biology underlying this in many instances remains unclear.

• Age

As true in any atherosclerotic diseases, older age is one of the strongest risk factors of PAD. For example, in the NHANES, the prevalence of PAD was ~15% in individuals aged 70 years or older but ~1% in those aged 40–49 years.[38] In most racial and ethnic groups, the prevalence of PAD approximately doubles with each subsequent decade of life beginning with those aged 40–49 year.[36] This why the AHA/ACC 2016 PAD Guideline recommends screening of PAD using the ABI in adults aged 65 years or older (and younger adults according to other risk factors).[1]

• Sex

Until the age of ~60–70 years, at a given age, male sex is known to have a higher risk of atherosclerotic diseases such as CAD and stroke compared to the female sex. However, several studies have shown that the prevalence of PAD is similar between men and women at any given age.[21, 33, 38, 39] This similar prevalence between men and women may partially reflect the property of ankle blood pressure potentially being lower in individuals at shorter heights. Indeed, some experts have proposed a sex-specific threshold of ABI for detecting PAD.[40] However, to our knowledge, major clinical guidelines have not adopted sex-specific thresholds of ABI and consistently recommend ABI ≤0.9 to identify PAD regardless of sex.[1, 41] Of note, a study including ~1,800 apparently healthy adults estimated that the potential impact of female sex on ABI is small (i.e., around −0.02) after accounting for other major demographic and clinical factors.[42]

- **Tobacco Use and Electronic Cigarettes**

  Smoking is one of the most important modifiable risk factors of atherosclerotic diseases. Its impact is particularly strong for PAD, and epidemiologic data have consistently shown current smoking is associated with a 2- to 3-fold increased risk of PAD.[33, 34, 43–45] A recent report from the Atherosclerosis Risk in Communities (ARIC) study demonstrated that the relative risk (RR) according to pack-years ≥25 (vs. never smokers) was ~4 for PAD and 1.5–2 for CAD and stroke.[46] This study also showed that the impact of smoking persisted up to 30 years for PAD, whereas the elevated risk returned to the level of never smokers within 20 years for other atherosclerotic diseases (Figure 1). Importantly, a recent Mendelian randomization analysis demonstrated that smoking is indeed more likely to cause PAD than CAD and stroke.[4748] Even among adolescents, cigarette smoking is associated with an increase in carotid intima-media thickness.[48] Therefore, we should continue our efforts for smoking prevention and cessation among all age groups. Also, any documents stating the impact of smoking on cardiovascular disease should take into account PAD; otherwise, the document would underestimate the harm of smoking on the cardiovascular system. Although long-term data are lacking, a body of evidence suggests potential harm of electronic cigarettes on the vascular system.[49–52]

- **Hypertension**

  According to its high prevalence and strong pathophysiological contribution, a study using data from the Health Professionals Follow-up Study estimated that hypertension accounts for ~40% of PAD risk. A study using data from ARIC recently quantified the association of the new hypertension classification according to the AHA/ACC 2017 Hypertension Guideline.[53, 54] This study demonstrates a dose-response relationship between systolic blood pressure and the risk of PAD, with a RR of ~2.6 if systolic blood pressure ≥140 mmHg and ~1.6 if systolic blood pressure 120–139 mmHg, compared to the reference <120 mmHg, among individuals not taking antihypertensive medications. On the other hand, the excess risk of PAD was only observed when diastolic blood pressure is ≥90 mmHg. This study with a long follow up over 25 years has uniquely shown that blood pressure (especially systolic) was robustly associated with incident CLTI.

- **Diabetes**

  Together with smoking, diabetes is considered one of the strongest risk factors for PAD.[55] Indeed, a meta-analysis demonstrated the highest odds ratio (OR) of having PAD for current smoking (OR 2.1) followed by diabetes (OR 1.7).[20] Of importance, diabetes is particularly strongly associated with a severe form of PAD. For example, a US cohort study has recently reported that the hazard ratio (HR) of CLTI was 10.3 (95% confidence interval [CI] 4.8–22.5) in middle-aged adults with diagnosed diabetes and hemoglobin A1c ≥7% compared to those with no diagnosis of diabetes and hemoglobin A1c <5.7%. Moreover, diabetes accounts for ~70% of cases undergoing lower extremity amputation in the US.[30]

- **Lipoproteins**

  Despite strong data linking low-density lipoprotein cholesterol (LDL-C) to CAD, few epidemiologic studies have demonstrated a link between LDL-C and incident PAD.[56, 57] In

ARIC each standard deviation increment in LDL-C was associated with CAD (HR, 1.20 [95% CI, 1.12–1.28]) but not PAD (HR, 1.10 [95% CI, 0.97–1.25].[58] Data from the Women's Health Study (WHS) similarly showed a strong risk association between LDL-C and incident CAD and cerebrovascular disease but not PAD.[59] In contrast, data from ARIC, WHS, and the Physicians' Health Study (PHS) have demonstrated a strong link between high-density lipoprotein cholesterol (HDL-C) and total cholesterol:HDL-C ratio measures and incident PAD.[56, 58, 59] Lipid subfraction analyses suggest that triglyceride-rich lipoprotein particles are the primary drivers of lipid-associated risk in PAD.[56, 58–66]

Epidemiologic data linking lipoprotein(a) to incident PAD are mixed. Data from several small studies have suggested a link between lipoprotein(a) and incident,[61] prevalent,[62] and worsening PAD.[63] However, there was not a significant association between lipoprotein(a) and incident PAD in either WHS[64] or PHS.[56] In contrast, GWAS data have demonstrated an association between lipoprotein(a) and PAD.[65] In the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome), the risk of PAD among participants in the placebo arm was associated with baseline lipoprotein(a) concentration rather than LDL-C.[66]

Emerging Risk Pathways

• Inflammation

Inflammation has emerged as an important risk marker of systemic atherosclerosis, and numerous studies have linked inflammation biomarkers with incident PAD. In a prospective, nested, case-control study from the PHS, which included apparently healthy men free of cardiovascular disease, baseline levels of C-reactive protein (CRP) were independently associated with incident PAD (adjusted HR extreme quartiles 2.2; 95% CI, 1.1–4.8; P=0.04). The risk association was even greater for individuals requiring lower extremity revascularization. Similar associations for CRP were demonstrated in the Edinburgh Artery Study and WHS.[64, 67] In ARIC, baseline high-sensitivity CRP concentration was associated with overall incident PAD (HR per standard deviation [log transformed] 1.34; 95% CI, 1.18–1.52) as well as incident CLTI (HR per standard deviation [log transformed] 1.34; 95% CI, 1.09–1.65).[68] Soluble intercellular adhesion molecule (sICAM)-1, a marker of leukocyte adhesion, was also associated with incident PAD in PHS (OR for highest vs. referent quartile 3.2; 95% CI, 1.4–7.4; P=0.008).[69]

• Thrombosis

Thrombosis has emerged as an important therapeutic target in PAD, and there are numerous studies suggesting a link between coagulation cascade activation and PAD. D-dimer, a fibrin degradation product release in the blood during fibrinolysis, is a common biomarker of thrombosis. Among 370 individuals with PAD defined by an abnormal ABI, D-dimer was independently and inversely associated with several measures of functional capacity, including 6-minute walk distance and 4-meter walking velocity.[70] In the Biomarker Risk Assessment in Vulnerable Outpatients (BRAVO) Study, which followed 595 subjects with PAD for up to 3 years, D-dimer levels rose 2 months prior to adverse CAD events compared

to individuals who did not suffer coronary events.[71] D-dimer also independently associates with adverse limb events,[72] severity of PAD,[73, 74] and polyvascular disease.[75]

Fibrinogen is an enzymatic target of thrombin also involved in clot formation. In a nested case-control study of previously healthy men in PHS, baseline fibrinogen concentration was associated with incident PAD (adjusted RR highest vs. referent quartile 2.2; 95% CI, 1.1–4.7; P=0.02).[56] Similarly, fibrinogen was associated with incident PAD in the Edinburgh Artery Study (RR 1.16; 95% CI, 1.05–1.17; P <0.01) and ARIC (RR highest vs. referent quartile 2.14; 95% [CI, 1.31–3.51; P=0.003) after adjusting for other cardiovascular risk factors.[76, 77] Finally, markers of impaired fibrinolysis, including raised levels of plasminogen activator inhibitor-1 and tissue plasminogen activator antigen, are also linked to PAD.[65, 78–80]

GWAS data have demonstrated a link between the Factor V Leiden variant and PAD.[65] Notably, this association has not been demonstrated for CAD. More recently, two randomized clinical trials have shown that the addition of low-dose rivaroxaban, a factor Xa inhibitor, to aspirin is effective at reducing limb events in patients with stable PAD[79] and in those following lower extremity revascularization.[80]

- **Platelet Activation**

Enhanced platelet activation may also contribute to the development of PAD, although data supporting this primarily come from small case-control studies. Compared to healthy control subjects, patients with both IC and CLTI exhibit greater expression of platelet P-selectin,[81, 82] a cell-surface adhesion molecule, as well as increased platelet aggregation,[81] and this is proportional to disease severity.[81] Individuals with PAD treated with the antiplatelet drug aspirin exhibit normal platelet aggregation, suggesting potential unresponsiveness to aspirin therapy in this population.[83] In the Edinburgh Artery Study, genetic variation in the platelet receptor GP IIIa locus was associated with a decreased incidence of IC over 5 years of follow-up.[84] More data are needed to determine whether there is a prospective link between platelet activation and incident PAD.

- **Microvascular Disease**

PAD has traditionally been recognized as a large artery disease. However, several recent studies have shown that microvascular disease may play an important role in the development and progression of PAD. For example, a US community-based cohort study with 9,371 adults has demonstrated that any retinopathy is associated with incident PAD and CLTI independently of other potential confounders such as diabetes and blood pressure.[85] Notably, this study has demonstrated that the HR according to any retinopathy was greater for CLTI and PAD (~3.4 and ~2.2, respectively) compared to stroke and CAD (<2). A similar pattern was shown for another measure of microvascular disease, albuminuria, in an international collaborative study including more than 800,000 individuals.[86] The robust association of retinopathy and nephropathy with lower extremity amputations was confirmed in US veterans.[87] Similarly, this study showed a stronger association between microvascular disease and amputation than major adverse cardiovascular events (MACE).

Biomarkers

Biomarkers have been widely used in cardiovascular medicine for disease diagnosis (e.g., high-sensitivity troponin for diagnosing acute myocardial infarction [MI]) and risk prediction (e.g., coronary artery calcium for guiding the intensity of lipid-lowering therapy). Although still exploratory, several potential biomarkers for PAD have been reported. For example, Wilson et al. conducted proteomic profiling in plasma samples from patients with PAD and persons without PAD and found that β2-microglobulin is uniquely elevated in the patients with PAD.[88] Another study also confirmed that β2-microglobulin is strongly and robustly associated with subsequent risk of PAD in the general population.[89] Also, biomarkers representing the pathophysiological pathways described above (e.g., hyperglycemia or inflammation) are likely to reflect the risk of PAD. Nonetheless, to our knowledge, to date, the most promising circulating biomarker of future PAD risk, especially its severe form, CLTI, is likely to be high-sensitivity cardiac troponin T (hs-cTnT). Specifically, a recent community-based study has found that individuals with hs-cTnT ≥14 ng/L had ~10-times (95% CI ~6 to ~15-times) higher risk of developing CLTI compared to those with hs-cTnT <3 ng/L after adjusting for various demographic and clinical covariates.[90] Corresponding relative risk was ~4 for hs-cTnT 9–13 ng/L, ~2.5 for 6–8 ng/L, and ~2 for 3–5 ng/L.

Complications

• Amputation

Although amputation is an important therapeutic option for severe cases of PAD, it remains a marker of poor cardiovascular outcomes. Among 186,338 Medicare recipients who underwent major lower extremity amputation from 2000–2008, mortality was 13.5% at 30 days, 48.3% at 1 year, and 70.9% at 3 years.[91] Above-the-knee amputation was more strongly associated with death than below-the-knee amputation (HR 1.31; 95% CI, 1.25–1.36). There remains significant geographic variation in amputation rates for PAD across the U.S.,[92] and both Black race and low socioeconomic status are associated with increased risk of amputation.[93]

• Acute Limb Ischemia

Contemporary epidemiologic data on in the incidence of ALI are limited. Over a one year period (1980) in Sweden, there were 138 ALI cases out of a population of 1.5 million individuals.[94] Overall mortality was 19.5% among those with ALI. National healthcare data from Scotland in the 1970s and 1980s report the incidence of ALI was 1:27,000.[95] Mortality was stable at 30% during the period of study. Among individuals residing in Gloucestershire, England, in 1994, ALI incidence was 1:7,000; this figure rose to 1:6,000 when cases of acute bypass graft occlusion were included.[96] Of note, although these studies document acute thrombotic limb occlusion, they do not specify the presence or absence of PAD.

Importantly, recent clinical trials have begun reporting ALI outcomes. For instance, the EUCLID (Examining Use of Ticagrelor in PAD) trial of 13,885 individuals with

symptomatic PAD reported 293 ALI events (0.8 per 100 patient-years).[97] 13% of those suffering ALI requiring major amputation. ALI was strongly associated with an increased risk of MACE (HR 1.4; 95% CI, 1.0–2.1; P=0.04), all-cause mortality (HR 3.3; 95% CI, 2.4–4.6; P<0.01), and major amputation (HR 34.2; 95% CI, 9.7–20.8; P<0.01). Similarly, among 3,787 subjects with symptomatic PAD in the Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis–Thrombolysis in Myocardial Infarction 50 (TRA2°P-TIMI 50), ALI occurred in 108 individuals at a rate of 1.3%/year.[98]

- **Mortality**

PAD is strongly linked with a heightened risk of death. According to the Centers for Disease Control and Prevention, in 2019 PAD was listed as the underlying cause of death in 11,753 individuals with 58,210 cases of any-mention deaths.[99, 100] A meta-analysis of 48,294 subjects from 16 prospective cohorts found a strong association between ABI and mortality.[101] The 10-year cardiovascular mortality for men with an ABI ≤0.90 compared to those with an ABI 1.11–1.40 was 18.7% vs. 4.4% (HR 2.9; 95% CI, 2.3–3.7) after adjusting for traditional atherosclerotic risk factors. In women, 10-year cardiovascular mortality was lower (12.6% vs. 4.1%) with a similar relative risk (HR 3.0; 95% CI, 2.0–4.4).[102] Although older data suggested PAD-related mortality was primarily due to cardiovascular causes, recent data suggest many patients with PAD die from cancer-related causes.[102]

Other CVDs

Since PAD is a subtype of atherosclerotic disease, it is not surprising that persons with PAD have a higher risk of other atherosclerotic diseases such as CAD and stroke.[103] Consequently, the AHA/ACC 2018 Cholesterol guideline acknowledges ABI ≤0.9 as a “risk enhancer” to be taken into account for guiding risk-based primary prevention beyond traditional atherosclerotic risk factors.[12]

This guideline takes into account symptomatic PAD (namely, a history of intermittent claudication with ABI <0.85 or lower extremity revascularization or amputation) as a type of major atherosclerotic CVD to classify patients with atherosclerotic CVD into very high-risk vs. high-risk for secondary prevention. Specifically, very high-risk is defined as a history of multiple major ASCVDs (namely, polyvascular disease) or one major ASCVD and multiple high-risk conditions such as older age or diabetes. The inclusion of symptomatic PAD in this classification is important since the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial[104] has demonstrated that the prognostic impact of symptomatic PAD is similar or even larger than that of MI or stroke. This observation highlights the importance of the concept of polyvascular disease.

Several studies have also demonstrated that individuals with PAD are at elevated risk of heart failure (HF).[105–107] For example, a report from ARIC, including 13,150 middle-aged US adults, showed that ABI ≤1.0 (vs. 1.01–1.40) conferred ~40% elevated risk of HF after accounting for potential confounders such as diabetes, smoking, and the presence of CAD or carotid atherosclerosis.[106] A recent report from the Multi-Ethnic Study of Atherosclerosis observed that the elevated risk related to low ABI was more evident for HF with reduced

ejection than HF with preserved ejection fraction.[107] These observations will have important clinical implications given a body of evidence showing reduced risk of HF by SGLT2 inhibitors regardless of diabetic status.

- **Physical function and quality of life**

A number of studies have shown that persons with PAD, regardless of the presence/absence or types of leg symptoms, have reduced physical function.[108–112] For example, one of the largest studies using data from ARIC showed that persons with ABI ≤0.9 (PAD) and those with ABI 0.9–1.0 (borderline low ABI) had 2-times higher odds of having impaired physical function defined as a reduced score of a validated instrument, the Short Physical Performance Battery (Figure 2) after accounting for various potential confounders such as a history of stroke or HF.

Several studies have also investigated the quality of life (QOL) related to PAD. In those studies, PAD is consistently associated with a reduction of the physical component of QOL (e.g., body pain or physical activity) regardless of age or geography of study populations.[113–116] In contrast, for the mental component of QOL, most studies showed no association or an association with a limited domain (e.g., vitality[113, 115]).

- **Cost**

Several studies have reported that PAD considerably increases medical expenditure. For example, a study using data from the Agency for Healthcare Research and Quality Medical Expenditure Panel Surveys has estimated that the average annual expenditure per individual was $11,553 (95%CI $8,137-$14,968) for patients with PAD vs. $4,219 (95% CI, $4,064-$4,375) for those without.[117] Increased prescription medication, inpatient care, and outpatient care all contributed to the higher medical expenditure in patients with PAD. The medical expenditure is particularly high in patients with severe PAD requiring major amputation. For example, a study using data from Medicare estimated that the annual average medical expenditure was $55,700 per patient after the procedure.[118]

Polyvascular Disease

Historically, patients with PAD were frequently recruited to clinical trials of atherosclerotic therapies because of their high risk for cardiovascular outcomes. However, outcomes were rarely reported in subgroups of individuals with PAD alone or polyvascular disease, and clinical guidelines recommended near uniform treatment of atherosclerotic risk factors regardless of the affected arterial bed. This began to change when early insights from clinical registries identified a greater risk for polyvascular disease.[119, 120] Polyvascular disease is also an ideal opportunity for personalized medicine, as the potential tradeoffs of any given therapy, particularly novel antiplatet and antithrombotic regimens with higher bleeding risk, may be more acceptable in this patient population (Figure 3).

Few studies have examined risk factors associated with developing polyvascular disease. Using 2-sample Mendelian randomization in individuals with PAD as well as CAD, cerebrovascular disease, or abdominal aortic aneurysm, investigators sought to determine whether a causal link existed between atherogenic lipoproteins, blood pressure, glycated

hemoglobin, and smoking.[121] Genetically-predicted levels of small, dense LDL particles as well as systolic blood pressure were most strongly associated with polyvascular disease, although the analysis was limited by small sample size (n=2009).[65, 122] Genomic analyses have demonstrated that variants in the chromosome 9p21 locus are associated with not only CAD and cerebrovascular disease but also a diagnosis of PAD[65] and low ABI measures.[122]

Several clinical studies have documented an increased cardiovascular risk associated with polyvascular disease (Table 3). For instance, among 68,236 patients with a history of atherosclerotic disease or ≥3 atherosclerotic risk factors in the Reduction of Atherothrombosis for Continued Health (REACH) Registry, polyvascular disease was independently associated with an increased risk of MACE (HR 1.99; 95% CI, 1.78–2.24; P<0.001) and was a stronger risk marker than diabetes or a history of ischemic event in the prior year. In FOURIER, patients with polyvascular PAD were at highest risk of MACE among subjects in the placebo arm: MI or stroke only (Kaplan-Meier incidence rate at 30 months 7.6%), PAD only (10.3%), PAD + MI (14.9%).[104] Subsequent studies have shown that diabetes further amplifies risk of cardiovascular events among patients with polyvascular disease.[123–125]

Recently, an analysis of 943,232 individuals from the MarketScan and Medicare databases demonstrated an increased incidence of atherosclerotic events (MI, coronary revascularization, stroke, carotid revascularization, ALI, peripheral artery revascularization, or major amputation) among patients with polyvascular disease: 1 bed (event rate per 1,000 person-years 40.8; 95% CI, 33.2–36.2), 2 bed (68.9; 95% CI, 67.9–70.0), 3 bed (119.5; 95% CI, 117.0–122.0).[126] PAD had an equivalent prognostic impact, if not greater, than CAD or cerebrovascular disease: PAD + CAD (event rate of atherosclerotic cardiovascular disease per 1,000 person-years 72.8; 95% CI, 71.0–74.7), PAD + cerebrovascular disease (63.9; 95% CI, 60.6–67.4), CAD + cerebrovascular disease (67.9; 95% CI, 66.4–69.3). Additionally, although atherosclerotic disease in a given bed was most strongly associated with its respective endpoint (e.g. CAD with MI, cerebrovascular disease with stroke, and PAD with limb events), all atherosclerotic endpoints were associated with polyvascular disease.

Future Directions

PAD has received greater attention in recent years, both in epidemiologic research and cardiovascular outcome trials, and we expect this will further our understanding of PAD development in the near future. Already, large cohorts such as the UK Biobank and the Million Veterans Program have yielded important insights into the genomic basis of PAD (detailed elsewhere in this issue).[65] Transcriptomic analysis of patients with PAD undergoing lower extremity revascularization can identify markers of future adverse events, and this technology potentially has the ability to identify risk markers of PAD subtypes, such as macrovascular versus microvascular disease as well as CLTI.[127] Finally, recent randomized, placebo-controlled trials have demonstrated a benefit of anti-inflammatory therapy in reducing cardiovascular events,[128, 129] and preliminary data suggest such a strategy may also be effective in PAD.[130] We hope future trials will help advance our understanding of the role inflammation plays in PAD and polyvascular disease development.

Conclusions

PAD is associated with exertional limb symptoms, functional decline, and poor quality of life, and individuals with PAD at heightened risk of lower extremity ulceration, amputation, and death. The global prevalence of PAD continues to grow in parallel with the expanding burden of atherosclerotic risk factors and an aging population. Although many risk factors of PAD are shared with other cardiovascular diseases, some risk factors, such as smoking and dyslipidemia, have a differential impact on PAD risk compared to that of CAD. Increased focus on PAD, particularly in the setting of polyvascular disease, has furthered our understanding of atherosclerotic risk, and this paradigm is increasingly used in the design of cardiovascular therapeutic trials. We feel this focus is long overdue and is necessary to help us increase PAD awareness, detection, and management in the future.

Sources of Funding

This work was supported by NIH K23 HL151871 (Dr. Aday).

Disclosures

Dr. Aday reports receiving consulting fees from OptumCare outside of the submitted work. Dr. Matsushita received research funding from NIH and Kyowa Kirin and personal fees from Fukuda Denshi and Kyowa Kirin outside of the submitted work.

Non-standard Abbreviations and Acronyms

ABI	ankle-brachial index
ALI	acute limb ischemia
ARIC	Atherosclerosis Risk in Communities Study
BMI	body mass index
CAD	coronary artery disease
CI	confidence interval
CLTI	chronic limb-threatening ischemia
EUCLID	Examining Use of Ticagrelor in Peripheral Artery Disease
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio
IC	intermittent claudication
LDL-C	low-density lipoprotein cholesterol

MACE	major adverse cardiovascular events
MI	myocardial infarction
NIS	Nationwide Inpatient Sample
OR	odds ratio
PAD	peripheral artery disease
PEGASUS	Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin
PHS	Physicians' Health Study
REACH	Reduction of Atherothrombosis for Continued Health
RR	relative risk
WHS	Women's Health Study

References

1. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e726–e779. [PubMed: 27840333]
2. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res. 2015;116:1509–1526. [PubMed: 25908725]
3. Olin JW. Thromboangiitis obliterans (Buerger's disease). N Engl J Med. 2000;343:864–9. [PubMed: 10995867]
4. Saadoun D, Vautier M, Cacoub P. Medium- and Large-Vessel Vasculitis. Circulation. 2021;143:267–282. [PubMed: 33464968]
5. Gornik HL, Persu A, Adlam D, Aparicio LS, Azizi M, Boulanger M, et al. First International Consensus on the diagnosis and management of fibromuscular dysplasia. Vasc Med. 2019;24:164–189. [PubMed: 30648921]
6. Schorr EN, Treat-Jacobson D. Methods of symptom evaluation and their impact on peripheral artery disease (PAD) symptom prevalence: a review. Vasc Med. 2013;18:95–111. [PubMed: 23509087]
7. Pradhan AD, Aday AW, Beckman JA. The Big MAC Attack on Peripheral Artery Disease. Circulation. 2020;141:1211–1213. [PubMed: 32282252]
8. Hiatt WR, Armstrong EJ, Larson CJ, Brass EP. Pathogenesis of the Limb Manifestations and Exercise Limitations in Peripheral Artery Disease. Circ Res. 2015;116:1527–1539. [PubMed: 25908726]
9. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg. 2019;69:3S–125S.e40. [PubMed: 31159978]
10. Gutierrez JA, Aday AW, Patel MR, Jones WS. Polyvascular Disease: Reappraisal of the Current Clinical Landscape. Circ Cardiovasc Interv. 2019;12:e007385. [PubMed: 31833412]
11. Aboyans V Polyvascular Disease: Definition, Epidemiology, Relevance. In: Lanzer P, ed. PanVascular Medicine. Berlin: Springer; 2015: 4779–4810.
12. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American

Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1082–e1143. [PubMed: 30586774]

13. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126:2890–2909. [PubMed: 23159553]
14. Ouriel K, Zarins CK. Doppler ankle pressure: an evaluation of three methods of expression. Arch Surg. 1982;117:1297–1300. [PubMed: 7125893]
15. Ouriel K, McDonnell AE, Metz CE, Zarins CK. Critical evaluation of stress testing in the diagnosis of peripheral vascular disease. Surgery. 1982;91:686–693. [PubMed: 7079971]
16. Xu D, Li J, Zou L, Xu Y, Hu D, Pagoto SL, Ma Y. Sensitivity and specificity of the ankle--brachial index to diagnose peripheral artery disease: a structured review. Vasc Med. 2010;15:361–369. [PubMed: 20926495]
17. Aday AW, Kinlay S, Gerhard-Herman MD. Comparison of different exercise ankle pressure indices in the diagnosis of peripheral artery disease. Vasc Med. 2018;23:541–548. [PubMed: 29992854]
18. Misra S, Shishehbor MH, Takahashi EA, Aronow HD, Brewster LP, Bunte MC, et al. Perfusion Assessment in Critical Limb Ischemia: Principles for Understanding and the Development of Evidence and Evaluation of Devices: A Scientific Statement From the American Heart Association. Circulation. 2019;140:e657–e672. [PubMed: 31401843]
19. Song P, Fang Z, Wang H, Cai Y, Rahimi K, Zhu Y, et al. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. Lancet Glob Health. 2020;8:e721–e729. [PubMed: 32353319]
20. Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382:1329–1340. [PubMed: 23915883]
21. Allison MA, Cushman M, Solomon C, Aboyans V, McDermott MM, Goff DC, et al. Ethnicity and risk factors for change in the ankle-brachial index: The Multi-Ethnic Study of Atherosclerosis. J Vasc Surg. 2009;50:1049–1056. [PubMed: 19628357]
22. Pande RL, Perlstein TS, Beckman JA, Creager MA. Secondary prevention and mortality in peripheral artery disease: National Health and Nutrition Examination Study, 1999 to 2004. Circulation. 2011;124:17–23. [PubMed: 21690489]
23. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and Trends in Diabetes Among Adults in the United States, 1988–2012. JAMA. 2015;314:1021–1029. [PubMed: 26348752]
24. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart Disease and Stroke Statistics-2021 Update: A Report From the American Heart Association. Circulation. 2021;143:e254–e743. [PubMed: 33501848]
25. United States Census Bureau. Ortman JM, Velkoff VA, Hogan H An Aging Nation: The Older Population in the United States. 2014:25–1140.
26. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, et al. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. J Vasc Surg. 2014.
27. Agarwal SK, Wruck L, Quibrera M, Matsushita K, Loehr LR, Chang PP, et al. Temporal Trends in Hospitalizations for Acute Decompensated Heart Failure in the U.S.: Calibration using The Atherosclerosis Risk in Communities (ARIC) Surveillance Study. Circulation. 2014;129:AP024.
28. Goodney PP, Beck AW, Nagle J, Welch HG, Zwolak RM. National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. J Vasc Surg. 2009;50:54–60. [PubMed: 19481407]
29. Goodney PP, Tarulli M, Faerber AE, Schanzer A, Zwolak RM. Fifteen-year trends in lower limb amputation, revascularization, and preventive measures among medicare patients. JAMA Surg. 2015;150:84–86. [PubMed: 25409197]
30. Geiss LS, Li Y, Hora I, Albright A, Rolka D, Gregg EW. Resurgence of Diabetes-Related Nontraumatic Lower Extremity Amputation in the Young and Middle-Aged Adult U.S. Population. Diabetes Care. 2019;42:50–54. [PubMed: 30409811]
31. Cai M, Xie Y, Bowe B, Gibson AK, Zayed MA, Li T, et al. Temporal Trends in Incidence Rates of Lower Extremity Amputation and Associated Risk Factors Among Patients Using Veterans Health

Administration Services From 2008 to 2018. JAMA Netw Open. 2021;4:e2033953. [PubMed: 33481033]

32. Eid MA, Mehta KS, Goodney PP. Epidemiology of peripheral artery disease. Semin Vasc Surg. 2021;34:38–46. [PubMed: 33757634]
33. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. Circulation. 1993;88:837–845. [PubMed: 8353913]
34. Allison MA, Criqui MH, McClelland RL, Scott JM, McDermott MM, Liu K, et al. The Effect of Novel Cardiovascular Risk Factors on the Ethnic-Specific Odds for Peripheral Arterial Disease in the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Coll Cardiol. 2006;48:1190–1197. [PubMed: 16979004]
35. Criqui MH, Vargas V, Denenberg JO, Ho E, Allison M, Langer RD, et al. Ethnicity and peripheral arterial disease: the San Diego Population Study. Circulation. 2005;112:2703–2707. [PubMed: 16246968]
36. Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, Fabsitz RR, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. Am J Prev Med. 2007;32:328–333. [PubMed: 17383564]
37. Matsushita K, Sang Y, Ning H, Ballew SH, Chow EK, Grams ME, et al. Lifetime Risk of Lower-Extremity Peripheral Artery Disease Defined by Ankle-Brachial Index in the United States. J Am Heart Assoc. 2019;8:e012177. [PubMed: 31500474]
38. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. Circulation. 2004;110:738–743. [PubMed: 15262830]
39. McDermott MM, Liu K, Criqui MH, Ruth K, Goff D, Saad MF, et al. Ankle-Brachial Index and Subclinical Cardiac and Carotid Disease: The Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol. 2005;162:33–41. [PubMed: 15961584]
40. Kapoor R, Ayers C, Visotcky A, Mason P, Kulinski J. Association of sex and height with a lower ankle brachial index in the general population. Vasc Med. 2018;23:534–540. [PubMed: 29865989]
41. Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39:763–816. [PubMed: 28886620]
42. Aboyans V, Criqui MH, McClelland RL, Allison MA, McDermott MM, Goff DC Jr., et al. Intrinsic contribution of gender and ethnicity to normal ankle-brachial index values: the Multi-Ethnic Study of Atherosclerosis (MESA). J Vasc Surg. 2007;45:319–327. [PubMed: 17264011]
43. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. Circulation. 1997;96:44–49. [PubMed: 9236415]
44. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW. Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. Am Heart J. 2002;143:961–965. [PubMed: 12075249]
45. Meijer WT, Grobbee DE, Hunink MG, Hofman A, Hoes AW. Determinants of peripheral arterial disease in the elderly: the Rotterdam study. Arch Intern Med. 2000;160:2934–2938. [PubMed: 11041900]
46. Ding N, Sang Y, Chen J, Ballew SH, Kalbaugh CA, Salameh MJ, et al. J Am Coll Cardiol. 2019;74:498–507. [PubMed: 31345423]
47. Levin MG, Klarin D, Assimes TL, Freiberg MS, Ingelsson E, Lynch J, et al. Genetics of Smoking and Risk of Atherosclerotic Cardiovascular Diseases: A Mendelian Randomization Study. JAMA Netw Open. 2021;4:e2034461. [PubMed: 33464320]
48. Dratva J, Probst-Hensch N, Schmidt-Trucksäss A, Caviezel S, de Groot E, Bettschart R, et al. Atherogenesis in youth--early consequence of adolescent smoking. Atherosclerosis. 2013;230:304–309. [PubMed: 24075761]

49. Shahandeh N, Chowdhary H, Middlekauff HR. Vaping and cardiac disease. Heart. 2021;heartjnl-2020–318150.
50. Franzen KF, Willig J, Cayo Talavera S, Meusel M, Sayk F, Reppel M, et al. E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: A randomized, double-blinded pilot study. Vasc Med. 2018;23:419–425. [PubMed: 29985113]
51. Stokes AC, Xie W, Wilson AE, Yang H, Orimoloye OA, Harlow AF, et al. Association of Cigarette and Electronic Cigarette Use Patterns With Levels of Inflammatory and Oxidative Stress Biomarkers Among US Adults: Population Assessment of Tobacco and Health Study. Circulation. 2021;143:869–871. [PubMed: 33390037]
52. Fetterman JL, Keith RJ, Palmisano JN, McGlasson KL, Weisbrod RM, Majid S, et al. Alterations in Vascular Function Associated With the Use of Combustible and Electronic Cigarettes. J Am Heart Assoc. 2020;9:e014570. [PubMed: 32345096]
53. Lu Y, Ballew SH, Tanaka H, Szklo M, Heiss G, Coresh J, et al. 2017 ACC/AHA blood pressure classification and incident peripheral artery disease: The Atherosclerosis Risk in Communities (ARIC) Study. Eur J Prev Cardiol. 2020;27:51–59. [PubMed: 31362534]
54. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Himmelfarb C Dennison, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;138:e426–e483. [PubMed: 30354655]
55. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care. 2003;26:3333–3341. [PubMed: 14633825]
56. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA. 2001;285:2481–2485. [PubMed: 11368701]
57. Kennedy M, Solomon C, Manolio TA, Criqui MH, Newman AB, Polak JF, et al. Risk factors for declining ankle-brachial index in men and women 65 years or older: the Cardiovascular Health Study. Arch Intern Med. 2005;165:1896–1902. [PubMed: 16157835]
58. Kou M, Ding N, Ballew SH, Salameh MJ, Martin SS, Selvin E, et al. Conventional and Novel Lipid Measures and Risk of Peripheral Artery Disease. Arterioscler Thromb Vasc Biol. 2021;41:1229–1238. [PubMed: 33504178]
59. Aday AW, Lawler PR, Cook NR, Ridker PM, Mora S, Pradhan AD. Lipoprotein Particle Profiles, Standard Lipids, and Peripheral Artery Disease Incidence. Circulation. 2018;138:2330–2341. [PubMed: 30021845]
60. Duran EK, Aday AW, Cook NR, Buring JE, Ridker PM, Pradhan AD. Triglyceride-Rich Lipoprotein Cholesterol, Small Dense LDL Cholesterol, and Incident Cardiovascular Disease. J Am Coll Cardiol. 2020;75:2122–2135. [PubMed: 32354380]
61. Valentine RJ, Grayburn PA, Vega GL, Grundy SM. Lp(a) lipoprotein is an independent, discriminating risk factor for premature peripheral atherosclerosis among white men. Arch Intern Med. 1994;154:801–806. [PubMed: 8147686]
62. Dieplinger B, Lingenhel A, Baumgartner N, Poelz W, Dieplinger H, Haltmayer M, et al. Increased serum lipoprotein(a) concentrations and low molecular weight phenotypes of apolipoprotein(a) are associated with symptomatic peripheral arterial disease. Clin Chem. 2007;53:1298–1305. [PubMed: 17525104]
63. Aboyans V, Criqui MH, Denenberg JO, Knoke JD, Ridker PM, Fronek A. Risk factors for progression of peripheral arterial disease in large and small vessels. Circulation. 2006;113:2623–2629. [PubMed: 16735675]
64. Pradhan AD, Shrivastava S, Cook NR, Rifai N, Creager MA, Ridker PM. Symptomatic Peripheral Arterial Disease in Women: Nontraditional Biomarkers of Elevated Risk. Circulation. 2008;117:823–831. [PubMed: 18227386]
65. Klarin D, Lynch J, Aragam K, Chaffin M, Assimes TL, Huang J, et al. . Genome-wide association study of peripheral artery disease in the Million Veteran Program. Nat Med. 2019;25:1274–1279. [PubMed: 31285632]

66. Schwartz GG, Steg PG, Szarek M, Bittner VA, Diaz R, Goodman SG, et al. Peripheral Artery Disease and Venous Thromboembolic Events After Acute Coronary Syndrome. Circulation. 2020;141:1608–1617. [PubMed: 32223446]

67. Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GDO, Fowkes FGR. Inflammatory, haemostatic, and rheological markers for incident peripheral arterial disease: Edinburgh Artery Study. Eur Heart J. 2007;28:354–362. [PubMed: 17213229]

68. Ding N, Yang C, Ballew SH, Kalbaugh CA, McEvoy JW, Salameh M, et al. Fibrosis and Inflammatory Markers and Long-Term Risk of Peripheral Artery Disease: The ARIC Study. Arterioscler Thromb Vasc Biol. 2020;40:2322–2331. [PubMed: 32698688]

69. Pradhan AD, Rifai N, Ridker PM. Soluble Intercellular Adhesion Molecule-1, Soluble Vascular Adhesion Molecule-1, and the Development of Symptomatic Peripheral Arterial Disease in Men. Circulation. 2002;106:820–825. [PubMed: 12176954]

70. McDermott MM, Greenland P, Green D, Guralnik JM, Criqui MH, Liu K, et al. D-Dimer, Inflammatory Markers, and Lower Extremity Functioning in Patients With and Without Peripheral Arterial Disease. Circulation. 2003;107:3191–3198. [PubMed: 12810614]

71. McDermott MM, Liu K, Green D, Greenland P, Tian L, Kibbe M, et al. Changes in D-dimer and inflammatory biomarkers before ischemic events in patients with peripheral artery disease: The BRAVO Study. Vasc Med. 2016;21:12–20. [PubMed: 26647446]

72. Komarov A, Panchenko E, Dobrovolsky A, Karpov Y, Deev A, Titaeva E, et al. D-dimer and platelet aggregability are related to thrombotic events in patients with peripheral arterial occlusive disease. Eur Heart J. 2002;23:1309–16. [PubMed: 12175668]

73. Herren T, Stricker H, Haeberli A, Do DD, Straub PW. Fibrin formation and degradation in patients with arteriosclerotic disease. Circulation. 1994;90:2679–86. [PubMed: 7994808]

74. Cassar K, Bachoo P, Ford I, Greaves M, Brittenden J. Markers of coagulation activation, endothelial stimulation and inflammation in patients with peripheral arterial disease. Eur J Vasc Endovasc Surg. 2005;29:171–176. [PubMed: 15649725]

75. Panchenko E, Dobrovolsky A, Davletov K, Titaeva E, Kravets A, Podinovskaya J, et al. D-dimer and fibrinolysis in patients with various degrees of atherosclerosis. Eur Heart J. 1995;16:38–42.

76. Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Inflammatory, haemostatic, and rheological markers for incident peripheral arterial disease: Edinburgh Artery Study. Eur Heart J. 2007;28:354–362. [PubMed: 17213229]

77. Wattanakit K, Folsom AR, Selvin E, Weatherley BD, Pankow JS, Brancati FL, et al. Risk factors for peripheral arterial disease incidence in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Atherosclerosis. 2005;180:389–397. [PubMed: 15910867]

78. Smith FB, Lee AJ, Rumley A, Fowkes FG, Lowe GD. Tissue-plasminogen activator, plasminogen activator inhibitor and risk of peripheral arterial disease. Atherosclerosis. 1995;115:35–43. [PubMed: 7669086]

79. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391:219–229. [PubMed: 29132880]

80. Bonaca MP, Bauersachs RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. N Engl J Med. 2020;382:1994–2004. [PubMed: 32222135]

81. Rajagopalan S, McKay I, Ford I, Bachoo P, Greaves M, Brittenden J. Platelet activation increases with the severity of peripheral arterial disease: implications for clinical management. J Vasc Surg. 2007;46:485–90. [PubMed: 17826235]

82. Tan KT, Tayebjee MH, Lynd C, Blann AD, Lip GY. Platelet microparticles and soluble P selectin in peripheral artery disease: relationship to extent of disease and platelet activation markers. Ann Med. 2005;37:61–66. [PubMed: 15902848]

83. van Geffen JP, Kleinegris MC, Verdoold R, Baaten CC, Cosemans JM, Clemetson KJ, et al. Normal platelet activation profile in patients with peripheral arterial disease on aspirin. Thromb Res. 2015;135:513–520. [PubMed: 25600441]

84. Smith FB, Connor JM, Lee AJ, Cooke A, Lowe GD, Rumley A, et al. Relationship of the platelet glycoprotein PlA and fibrinogen T/G+1689 polymorphisms with peripheral arterial disease and ischaemic heart disease. Thromb Res. 2003;112:209–216. [PubMed: 14987913]
85. Yang C, Kwak L, Ballew SH, Jaar BG, Deal JA, Folsom AR, et al. Retinal microvascular findings and risk of incident peripheral artery disease: An analysis from the Atherosclerosis Risk in Communities (ARIC) Study. Atherosclerosis. 2020;294:62–71. [PubMed: 31812251]
86. Matsushita K, Ballew SH, Coresh J, Arima H, Arnlov J, Cirillo M, et al. Measures of chronic kidney disease and risk of incident peripheral artery disease: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2017;5:718–728. [PubMed: 28716631]
87. Beckman JA, Duncan MS, Damrauer SM, Wells QS, Barnett JV, Wasserman DH, et al. Microvascular Disease, Peripheral Artery Disease, and Amputation. Circulation. 2019;140:449–458. [PubMed: 31280589]
88. Wilson AM, Kimura E, Harada RK, Nair N, Narasimhan B, Meng XY, et al. Beta2-microglobulin as a biomarker in peripheral arterial disease: proteomic profiling and clinical studies. Circulation. 2007;116:1396–1403. [PubMed: 17724262]
89. Yang C, Kwak L, Ballew SH, Garimella PS, Jaar BG, Folsom AR, et al. Kidney function, bone-mineral metabolism markers, and future risk of peripheral artery disease. Atherosclerosis. 2017;267:167–174. [PubMed: 28992939]
90. Matsushita K, Kwak L, Yang C, Pang Y, Ballew SH, Sang Y, et al. High-sensitivity cardiac troponin and natriuretic peptide with risk of lower-extremity peripheral artery disease: the Atherosclerosis Risk in Communities (ARIC) Study. Eur Heart J. 2018;39:2412–2419. [PubMed: 29579246]
91. Jones WS, Patel MR, Dai D, Vemulapalli S, Subherwal S, Stafford J, et al. High mortality risks after major lower extremity amputation in Medicare patients with peripheral artery disease. Am Heart J. 2013;165:809–815, 815.e1. [PubMed: 23622919]
92. Jones WS, Patel MR, Dai D, Subherwal S, Stafford J, Calhoun S, et al. Temporal trends and geographic variation of lower-extremity amputation in patients with peripheral artery disease: results from U.S. Medicare 2000–2008. J Am Coll Cardiol. 2012;60:2230–2236. [PubMed: 23103040]
93. Arya S, Binney Z, Khakharia A, Brewster LP, Goodney P, Patzer R, et al. Race and Socioeconomic Status Independently Affect Risk of Major Amputation in Peripheral Artery Disease. J Am Heart Assoc. 2018;7:e007425. [PubMed: 29330260]
94. Dryjski M, Swedenborg J. Acute ischemia of the extremities in a metropolitan area during one year. J Cardiovasc Surg (Torino). 1984;25:518–522.
95. Clason AE, Stonebridge PA, Duncan AJ, Nolan B, Jenkins AM, Ruckley CV. Acute ischaemia of the lower limb: the effect of centralizing vascular surgical services on morbidity and mortality. Br J Surg. 1989;76:592–593. [PubMed: 2758265]
96. Davies B, Braithwaite BD, Birch PA, Poskitt KR, Heather BP, Earnshaw JJ. Acute leg ischaemia in Gloucestershire. Br J Surg. 1997;84:504–508. [PubMed: 9112902]
97. Hess CN, Huang Z, Patel MR, Baumgartner I, Berger JS, Blomster JI, et al. Acute Limb Ischemia in Peripheral Artery Disease. Circulation. 2019;140:556–565. [PubMed: 31238713]
98. Bonaca MP, Gutierrez JA, Creager MA, Scirica BM, Olin J, Murphy SA, et al. Acute Limb Ischemia and Outcomes With Vorapaxar in Patients With Peripheral Artery Disease. Circulation. 2016;133:997–1005. [PubMed: 26826179]
99. Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System: public use data file documentation: mortality multiple cause-of-death micro-data files. Accessed March 1, 2021. https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm
100. Centers for Disease Control and Prevention. CDC WONDER online database. March 2021. December 2018. Accessed March 1, 2021. https://wonder.cdc.gov/ucd-icd10.html.
101. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300:197–208. [PubMed: 18612117]

102. Rantner B, Kollerits B, Pohlhammer J, Stadler M, Lamina C, Peric S, et al. The fate of patients with intermittent claudication in the 21st century revisited – results from the CAVASIC Study. Sci Rep. 2017;7:45833.
103. Heald CL, Fowkes FG, Murray GD, Price JF. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: Systematic review. Atherosclerosis. 2006;189:61–9. [PubMed: 16620828]
104. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, et al. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). Circulation. 2018;137:338–350. [PubMed: 29133605]
105. Nishimura H, Miura T, Minamisawa M, Ueki Y, Abe N, Hashizume N, et al. Prognostic value of ankle brachial index for future incident heart failure in patients without previous heart failure: data from the impressive predictive value of ankle brachial index for clinical long term outcome in patients with cardiovascular disease examined by ABI study. Heart Vessels. 2017;32:295–302. [PubMed: 27412398]
106. Gupta DK, Skali H, Claggett B, Kasabov R, Cheng S, Shah AM, et al. Heart failure risk across the spectrum of ankle-brachial index: the ARIC study (Atherosclerosis Risk In Communities). JACC Heart Fail. 2014;2:447–454. [PubMed: 25194293]
107. Prasada S, Shah SJ, Michos ED, Polak JF, Greenland P. Ankle-brachial index and incident heart failure with reduced versus preserved ejection fraction: The Multi-Ethnic Study of Atherosclerosis. Vasc Med. 2019;24:501–510. [PubMed: 31480898]
108. Matsushita K, Ballew SH, Sang Y, Kalbaugh C, Loehr LR, Hirsch AT, et al. Ankle-brachial index and physical function in older individuals: The Atherosclerosis Risk in Communities (ARIC) study. Atherosclerosis. 2017;257:208–215. [PubMed: 28012644]
109. McDermott MM, Applegate WB, Bonds DE, Buford TW, Church T, Espeland MA, et al. Ankle brachial index values, leg symptoms, and functional performance among community-dwelling older men and women in the lifestyle interventions and independence for elders study. J Am Heart Assoc. 2013;2:e000257. [PubMed: 24222666]
110. McDermott MM, Fried L, Simonsick E, Ling S, Guralnik JM. Asymptomatic peripheral arterial disease is independently associated with impaired lower extremity functioning: the women's health and aging study. Circulation. 2000;101:1007–1012. [PubMed: 10704168]
111. McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, et al. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. JAMA. 2001;286:1599–1606. [PubMed: 11585483]
112. McDermott MM, Guralnik JM, Tian L, Liu K, Ferrucci L, Liao Y, et al. Associations of borderline and low normal ankle-brachial index values with functional decline at 5-year follow-up: the WALCS (Walking and Leg Circulation Study). J Am Coll Cardiol. 2009;53:1056–1062. [PubMed: 19298919]
113. Wu A, Coresh J, Selvin E, Tanaka H, Heiss G, Hirsch AT, et al. Lower Extremity Peripheral Artery Disease and Quality of Life Among Older Individuals in the Community. J Am Heart Assoc. 2017;6:e004519. [PubMed: 28108464]
114. Breek JC, Hamming JF, De Vries J, Aquarius AE, van Berge Henegouwen DP. Quality of life in patients with intermittent claudication using the World Health Organisation (WHO) questionnaire. Eur J Vasc Endovasc Surg. 2001;21:118–122. [PubMed: 11237783]
115. Regensteiner JG, Hiatt WR, Coll JR, Criqui MH, Treat-Jacobson D, McDermott MM, et al. The impact of peripheral arterial disease on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program. Vasc Med. 2008;13:15–24. [PubMed: 18372434]
116. Korhonen PE, Seppala T, Kautiainen H, Jarvenpaa S, Aarnio PT, Kivela SL. Ankle-brachial index and health-related quality of life. Eur J Prev Cardiol. 2012;19:901–907. [PubMed: 21835871]
117. Scully RE, Arnaoutakis DJ, DeBord Smith A, Semel M, Nguyen LL. Estimated annual health care expenditures in individuals with peripheral arterial disease. J Vasc Surg. 2018;67:558–567. [PubMed: 28847660]

118. Mustapha JA, Katzen BT, Neville RF, Lookstein RA, Zeller T, Miller LE, et al. Determinants of Long-Term Outcomes and Costs in the Management of Critical Limb Ischemia: A Population-Based Cohort Study. J Am Heart Assoc. 2018;7:e009724. [PubMed: 30369325]
119. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas J-L, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006;295:180–189. [PubMed: 16403930]
120. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA. 2010;304:1350–1357. [PubMed: 20805624]
121. Dikilitas O, Satterfield BA, Kullo IJ. Risk Factors for Polyvascular Involvement in Patients With Peripheral Artery Disease: A Mendelian Randomization Study. J Am Heart Assoc. 2020;9:e017740. [PubMed: 33287626]
122. Murabito JM, White CC, Kavousi M, Sun YV, Feitosa MF, Nambi V, et al. Association Between Chromosome 9p21 Variants and the Ankle-Brachial Index Identified by a Meta-Analysis of 21 Genome-Wide Association Studies. Circ Cardiovasc Genet. 2012;5:100–112. [PubMed: 22199011]
123. Gutierrez JA, Scirica BM, Bonaca MP, Steg PG, Mosenzon O, Hirshberg B, et al. Prevalence and Outcomes of Polyvascular (Coronary, Peripheral, or Cerebrovascular) Disease in Patients With Diabetes Mellitus (From the SAVOR-TIMI 53 Trial). Am J Cardiol. 2019;123:145–152. [PubMed: 30366601]
124. Verma S, Bhatt DL, Bain SC, Buse JB, Mann JFE, Marso SP, et al. Effect of Liraglutide on Cardiovascular Events in Patients With Type 2 Diabetes Mellitus and Polyvascular Disease: Results of the LEADER Trial. Circulation. 2018;137:2179–2183. [PubMed: 29760228]
125. Bonaca MP, Gutierrez JA, Cannon C, Giugliano R, Blazing M, Park JG, et al. Polyvascular disease, type 2 diabetes, and long-term vascular risk: a secondary analysis of the IMPROVE-IT trial. Lancet Diabetes Endocrinol. 2018;6:934–943. [PubMed: 30396865]
126. Colantonio LD, Hubbard D, Monda KL, Mues KE, Huang L, Dai Y, et al. Atherosclerotic Risk and Statin Use Among Patients With Peripheral Artery Disease. J Am Coll Cardiol. 2020;76:251–264. [PubMed: 32674789]
127. Newman JD, Cornwell MG, Zhou H, Rockman C, Heguy A, Suarez Y, et al. Gene Expression Signature in Patients With Symptomatic Peripheral Artery Disease. Arterioscler Thromb Vasc Biol. 2021; ATVBAHA.120.315857.
128. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med. 2020;383:1838–1847. [PubMed: 32865380]
129. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017;377:1119–1131. [PubMed: 28845751]
130. Russell KS, Yates DP, Kramer CM, Feller A, Mahling P, Colin L, et al. A randomized, placebo-controlled trial of canakinumab in patients with peripheral artery disease. Vasc Med. 2019;24:414–421. [PubMed: 31277561]
131. Bhatt DL, Peterson ED, Harrington RA, Ou FS, Cannon CP, Gibson CM, et al. Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes. Eur Heart J. 2009;30:1195–1202. [PubMed: 19339264]
132. Hirsh J, Bhatt DL. Comparative benefits of clopidogrel and aspirin in high-risk patient populations: lessons from the CAPRIE and CURE studies. Arch Intern Med. 2004;164:2106–2110. [PubMed: 15505123]
133. Bonaca M, Creager M, Olin J, Scirica B, Bohula E, Murphy S, et al. VORAPAXAR REDUCES PERIPHERAL REVASCULARIZATION REGARDLESS OF THE NUMBER OF DISEASED TERRITORIES: INSIGHTS FROM THE TRA2P-TIMI 50 TRIAL. J Am Coll Cardiol. 2013;61:E2018–E2018.
134. Bonaca MP, Bhatt DL, Storey RF, Steg PG, Cohen M, Kuder J, et al. Ticagrelor for Prevention of Ischemic Events After Myocardial Infarction in Patients With Peripheral Artery Disease. J Am Coll Cardiol. 2016;67:2719–2728. [PubMed: 27046162]

135. Gutierrez JA, Mulder H, Jones WS, Rockhold FW, Baumgartner I, Berger JS, et al. Polyvascular Disease and Risk of Major Adverse Cardiovascular Events in Peripheral Artery Disease: A Secondary Analysis of the EUCLID Trial. JAMA Netw Open. 2018;1:e185239. [PubMed: 30646395]

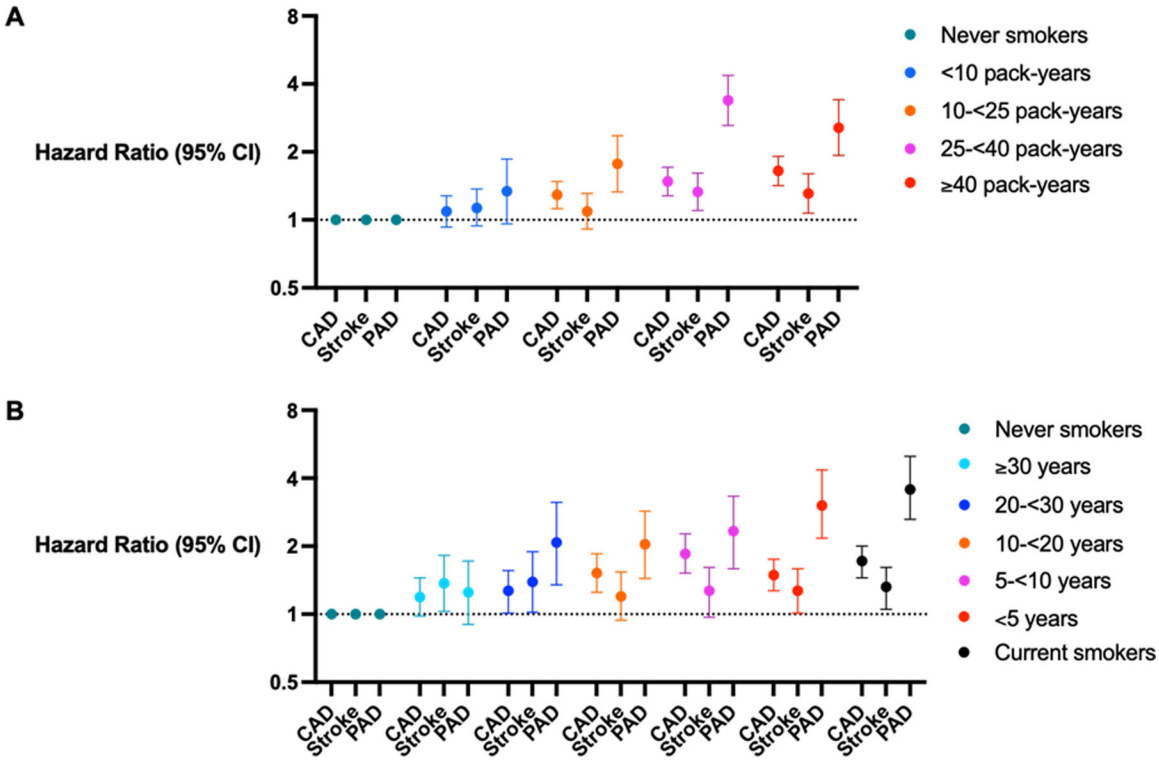

Figure 1. Risk of smoking and persistence of risk after cessation for major atherosclerotic diseases

A – Multivariable adjusted hazard ratios for CAD, stroke, and PAD by pack-years of smoking in the Atherosclerosis Risk in Communities Study. **B** – Time-varying multivariable adjusted hazard ratios for CAD, stroke, and PAD by time since smoking cessation in the Atherosclerosis Risk in Communities Study.

CAD refers to coronary artery disease; PAD, peripheral artery disease; CI, confidence interval

Data derived from Ding N, Sang Y, Chen J, Ballew SH, Kalbaugh CA, Salameh MJ, Blaha MJ, Allison M, Heiss G, Selvin E, Coresh J and Matsushita K. Cigarette Smoking, Smoking Cessation, and Long-Term Risk of 3 Major Atherosclerotic Diseases. *J Am Coll Cardiol.* 2019;74:498–507.

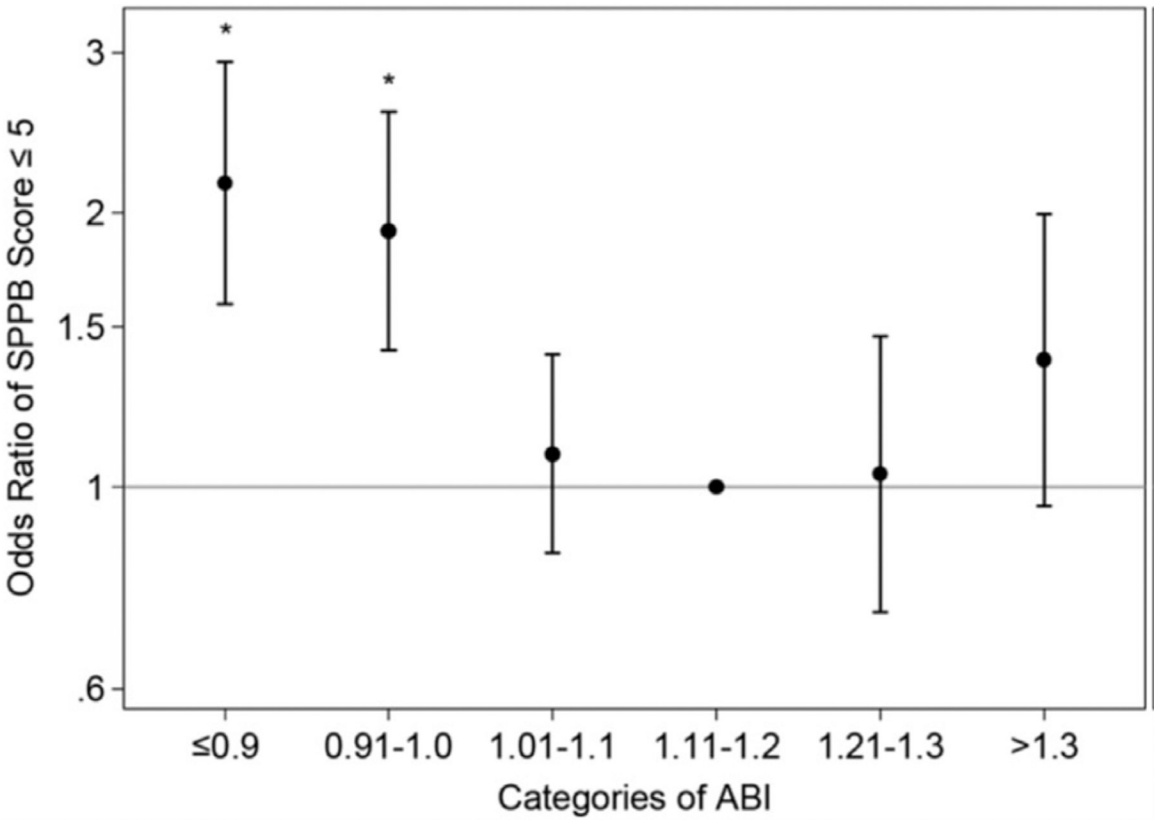

Figure 2. Adjusted odds ratio of reduced physical function* according to categories of ABI.

* Defined as the Short Physical Performance Battery score ≤5 and adjusted for age, race, sex, education, smoking, alcohol, body mass index, antihypertensive medications, systolic blood pressure, lipids, lipid-lowering medications, history of coronary artery disease, stroke, or heart failure.

ABI refers to ankle-brachial index.

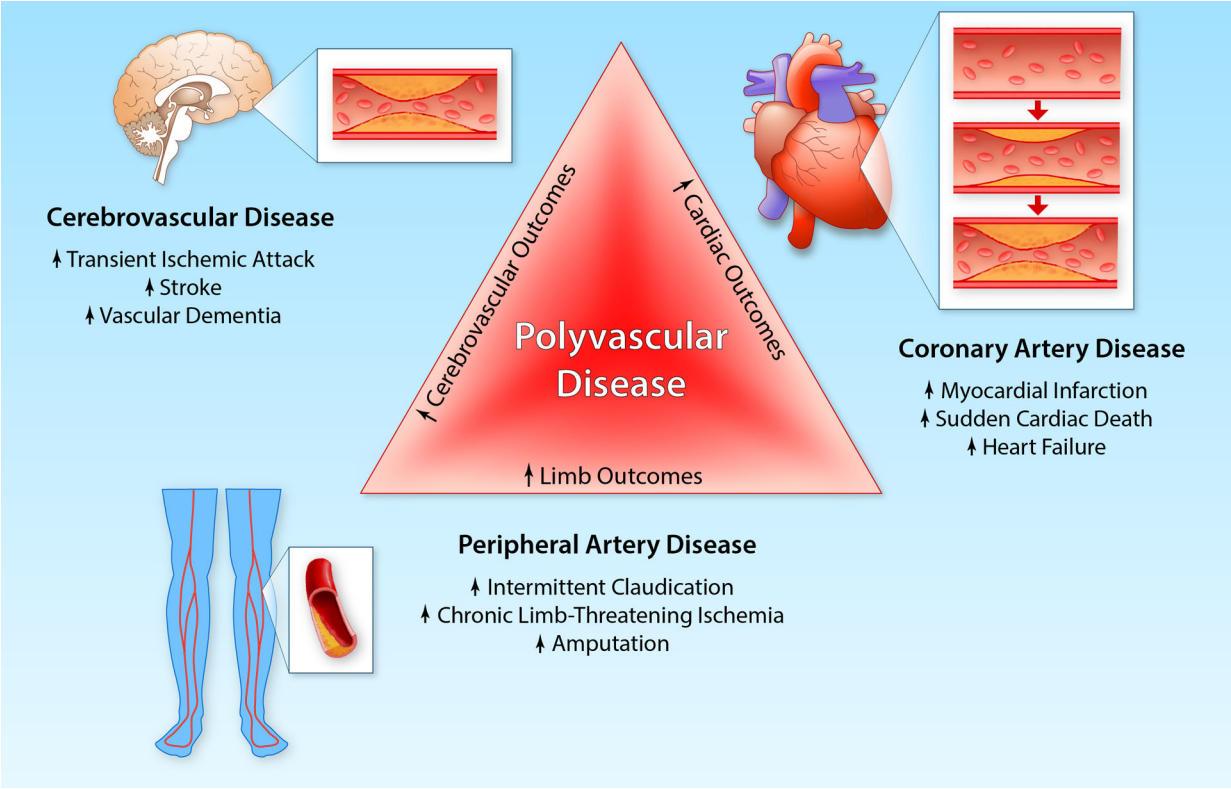

Figure 3. Cardiovascular Risks of Polyvascular Disease

Atherosclerotic disease in a given vascular bed is directly linked to adverse outcomes in that same organ. Because polyvascular disease is indicative of systemic atherosclerosis, individuals with polyvascular disease are at heightened risk for cardiovascular events in all vascular territories. (Illustration credit: Ben Smith).

Table 1.

Estimated global prevalence of peripheral artery disease in high-income and low- and middle-income countries

	Year of Estimation									Change over Time					
	2000 (millions)			2010 (millions)			2015 (millions)			2000–2010 (millions)			2000–2015 (millions)		
Age (years)	**HICs**	**LMICs**	**Global**	**HICs**	**LMICs**	**Global**	**HICs**	**LMICs**	**Global**	**HICs**	**LMICs**	**Global**	**HICs**	**LMICs**	**Global**
25–29	2.31	10.76	13.07	2.38	12.04	14.42	1.42	15.44	16.86	3.0	11.9	10.3	−38.6	43.5	29.0
30–34	2.80	11.47	14.27	2.76	12.34	15.10	1.86	15.56	17.43	−1.5	7.6	5.8	−33.6	35.7	22.1
35–39	3.49	11.25	14.73	3.34	13.78	17.12	2.38	15.75	18.13	−4.1	22.5	16.2	−31.7	40.0	23.1
40–44	4.07	11.14	15.21	3.94	14.71	18.65	3.09	17.25	20.34	−3.3	32.0	22.6	−24.1	54.9	33.7
45–49	4.53	11.41	15.94	4.85	14.35	19.21	3.89	18.20	22.09	7.1	25.8	20.5	−14.1	59.5	38.6
50–54	4.91	9.90	14.81	5.50	14.10	19.60	4.87	17.83	22.70	12.1	42.4	32.4	−0.8	80.1	53.3
55–59	4.53	9.11	13.64	5.95	14.17	20.12	5.72	16.65	22.37	31.3	55.5	47.5	26.3	82.7	64.0
60–64	5.34	9.07	14.42	6.24	11.79	18.03	6.46	16.18	22.63	16.8	29.9	25.1	20.9	78.3	57.0
65–69	5.29	8.42	13.70	5.55	10.12	15.67	7.22	12.61	19.83	4.9	20.3	14.3	36.6	49.8	44.7
70–74	5.59	6.95	12.55	6.04	9.02	15.06	6.82	9.89	16.70	8.0	29.7	20.1	21.9	42.2	33.1
75–79	4.81	4.96	9.77	5.37	7.01	12.38	6.81	8.12	14.93	11.7	41.4	26.8	41.6	63.7	52.8
80–84	3.11	3.02	6.12	4.72	4.40	9.12	6.05	5.22	11.27	52.0	45.8	48.9	94.7	73.1	84.1
85–89	2.25	1.41	3.66	3.03	2.09	5.12	4.52	2.68	7.19	34.8	47.9	39.8	101.2	89.9	96.6
≥90	1.17	0.54	1.72	1.61	0.86	2.47	2.99	1.16	4.15	37.2	58.8	44.1	154.7	113.2	141.7
Total	54.20	109.41	163.60	61.29	140.78	202.06	64.09	172.53	236.62	13.1	28.7	23.5	18.3	57.7	44.6

HICs refers to high-income countries; LMIC, low- and middle-income countries

Estimates derived from Song P, Fang Z, Wang H, Cai Y, Rahimi K, Zhu Y, Fowkes FGR, Fowkes FJI and Rudan I. Global and regional prevalence, burden, and risk factors for carotid atherosclerosis: a systematic review, meta-analysis, and modelling study. *The Lancet Global health.* 2020;8:e721-e729 and Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UKA, Williams LJ, Mensah GA and Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet (London, England).* 2013;382:1329–1340.

Table 2.

Association between modifiable cardiovascular risk factors and atherosclerotic diseases

Risk Factor	
Smoking	PAD > CAD/stroke
Diabetes	PAD > CAD/stroke
Low-Density Lipoprotein Cholesterol	PAD < CAD/stroke
Triglycerides	PAD > CAD/stroke
Hypertension	PAD = CAD/stroke*
Microvascular Disease	PAD > CAD/stroke

Table 2 displays the magnitude of risk associated with each risk factor for the components of polyvascular disease

PAD refers to peripheral artery disease; CAD, coronary artery disease

*Data suggest the risk association may be strongest for stroke

Table 3.

Cardiovascular Outcomes from Clinical Studies of Polyvascular Disease

Data Source	Study Type	Qualifying Vascular Territories	Patients with PAD/Total Sample (%)	Definition of MACEs	Impact on MACEs	Definition of MALEs	Impact on MALEs
CRUSADE[131]	Observational Registry	CAD – A or S PAD – S CVD – S	11,345/111,972 (10.1)	In-hospital mortality, MI, stroke, and HF	1 bed: OR 1.07 (95% CI, 1.02–1.12) 2 beds: OR 1.25 (95% CI, 1.18–1.33) 3 beds: OR 1.31 (95% CI, 1.15–1.46)	--	--
REACH[120]	Observational Registry	CAD – S PAD – S CVD – S	5,872/68,236 (8.6)	MI, stroke, or cardiovascular mortality	Polyvascular disease vs. atherosclerotic risk factors: HR 1.99 (95% CI, 1.78–2.24)	--	--
MarketScan + Medicare[126]	Observational Claims Data	CAD – A-S PAD – A-S CVD – A-S	156,129/943,232 (16.6)	MI, coronary revascularization, stroke, carotid revascularization, ALI, lower extremity revascularization, or amputation	2 vs. 1 bed: HR 1.45 (95% CI, 1.42–1.48) 3 vs. 1 bed: HR 2.08 (95% CI, 2.03–2.14)	ALI, lower extremity revascularization, or amputation	2 vs. 1 bed: HR 2.18 (95% CI, 2.02–2.36) 3 vs. 1 bed: HR 3.91 (95% CI, 3.58–4.28)
CAPRIE[132]	Randomized Controlled Trial	CAD – S PAD – S CVD – S	6,452/19,185 (33.6)	MI, stroke, or cardiovascular mortality	Polyvascular vs. single bed: RRR 12.4%; ARR 2.45%; NNT 41	--	--
TRA 2°P-TIMI 50[133]	Randomized Controlled Trial	CAD – S PAD – S CVD – S	3,787/26,449 (14.3)	MI, stroke, or cardiovascular mortality at 3 years	1 bed: 7.8% 2 beds: 14.7% 3 beds: 21.7%	Lower extremity revascularization	1 bed: 7.8% 2 beds: 14.7% 3 beds: 21.7%
FOURIER[104]	Randomized Controlled Trial	CAD – S PAD – S CVD – S	3,642/27,564 (13.2)	MI, stroke, or cardiovascular mortality	Kaplan-Meier incidence rate at 30 months PAD + MI or stroke: 14.9% PAD only: 10.3% MI or stroke only: 7.6%	--	--
PEGASUS-TIMI 54[134]	Randomized Controlled Trial	CAD – S PAD – A or S	1,143/21,162 (5.4)	MI, stroke, or cardiovascular mortality	PAD + CAD vs. PAD: HR 1.60 (95% CI, 1.20–2.13)	--	--
EUCLID[135]	Randomized Controlled Trial	CAD – S PAD – A or S CVD – S	13,885/13,885 (100.0)	MI, stroke, or cardiovascular mortality	PAD + cerebrovascular disease: HR 1.34 (95% CI, 1.15–1.57) PAD + CAD: HR 1.65 (95% CI, 1.43–1.91) PAD + CAD + cerebrovascular disease: HR 1.99 (95% CI, 1.69–2.34)	Lower extremity revascularization	PAD + CVD: HR 1.17 (95% CI, 1.02–1.35) PAD + CAD: HR 1.17 (95% CI, 1.03–1.34) PAD + CAD + CVD: HR 1.34 (95% CI, 1.15–1.57)
SAVOR-TIMI 53[123]	Randomized Controlled Trial	CAD – S PAD – S CVD – S	1,959/16,492 (11.9)	MI, stroke, or cardiovascular mortality	1 bed: HR 1.95 (95% CI, 1.63–2.35) 2 beds: HR 3.54 (95% CI, 2.84–4.43)	--	--

Data Source	Study Type	Qualifying Vascular Territories	Patients with PAD/Total Sample (%)	Definition of MACEs	Impact on MACEs	Definition of MALEs	Impact on MALEs
					3 beds: HR 4.64 (95% CI, 2.87–7.15)		
LEADER[124]	Randomized Controlled Trial	CAD – A,S PAD – S CVD – A or S	1,184/9,340 (12.7)	MI, stroke, or cardiovascular mortality	Polyvascular vs. single bed: HR 1.52 (95% CI, 1.33–1.73)	--	--
IMPROVE-IT[125]	Randomized Controlled Trial	CAD – S PAD – A or S CVD – S	1,005/18,144 (5.5)	MI, stroke, or cardiovascular mortality	Polyvascular vs. single bed: HR 1.55 (95% CI, 1.41–1.70)	Lower extremity revascularization	Polyvascular vs. single bed: HR 4.77 (95% CI, 3.75–6.06)
						Amputation	Polyvascular vs. single bed: HR 5.96 (95% CI, 2.74–12.94)

A refers to asymptomatic; A-S, symptoms not assessed in qualifying events; ALI, acute limb ischemia; ARR, absolute risk reduction; CAD, coronary artery disease; CAPRIE, Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events; CI, confidence interval; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines; CVD, cerebrovascular disease; EUCLID, Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; HF, heart failure; HR, hazard ratio; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Results; MACE, major adverse cardiovascular events; MALE, major adverse limb events; MI, myocardial infarction; OR, odds ratio; PAD refers to peripheral artery disease; PEGASUS-TIMI 54, Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin; REACH, Reduction of Atherothrombosis for Continued Health; RRR, relative risk reduction; S, symptomatic; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-TIMI 53; TRA2°P-TIMI 50=Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-TIMI 50