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Disclosures

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Lower Extremity Peripheral Artery Disease: Contemporary Epidemiology, Management Gaps, and Future Directions:

A Scientific Statement From the American Heart Association

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Abstract

Lower extremity peripheral artery disease (PAD) affects >230 million adults worldwide and is associated with increased risk of various adverse clinical outcomes (other cardiovascular diseases such as coronary heart disease and stroke and leg outcomes such as amputation). Despite its prevalence and clinical importance, PAD has been historically underappreciated by health care professionals and patients. This underappreciation seems multifactorial (eg, limited availability of the first-line diagnostic test, the ankle-brachial index, in clinics; incorrect perceptions that a leg vascular disease is not fatal and that the diagnosis of PAD would not necessarily change clinical practice). In the past several years, a body of evidence has indicated that these perceptions are incorrect. Several studies have consistently demonstrated that many patients with PAD are not receiving evidence-based therapies. Thus, this scientific statement provides an update for health care professionals regarding contemporary epidemiology (eg, prevalence, temporal trends, risk factors, and complications) of PAD, the present status of diagnosis (physiological tests and imaging modalities), and the major gaps in the management of PAD (eg, medications, exercise therapy, and revascularization). The statement also lists key gaps in research, clinical practice, and implementation related to PAD. Orchestrated efforts among different parties (eg, health care providers, researchers, expert organizations, and health care organizations) will be needed to increase the awareness and understanding of PAD and improve the diagnostic approaches, management, and prognosis of PAD.

Keywords

AHA Scientific Statements; diagnosis; epidemiology; peripheral artery disease; prognosis; risk factors

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Lower extremity peripheral artery disease (PAD) is atherosclerotic disease of the arteries supplying the legs.[1] Despite its prevalence and impact on adverse clinical outcomes, impaired physical function, and reduced physical activity, PAD has been understudied and underrecognized compared with other atherosclerotic diseases such as myocardial infarction and stroke.[2] The lack of awareness has led to underdiagnosis and undertreatment of PAD in the United States and around the world.[2]

There appear to be several reasons for this underrecognition of PAD. For example, the first-line method to diagnose PAD, the ankle-brachial index (ABI), is not readily available

in most clinics in the United States.[3] Also, many people think that leg diseases cannot be fatal, whereas myocardial infarction has been recognized as a leading cause of sudden cardiac death for a long time. Similarly, PAD is not widely recognized as a disabling condition, whereas stroke is established as the leading cause of disability. Difficulty walking, a hallmark of PAD-related disability, may be considered normal aging by clinicians, and the protean nature of ischemic leg symptoms can be mistaken for other diseases like arthritis or spinal degenerative disease. Also, some experts think that the specific investigation of PAD is not important, because evidence from myocardial infarction and stroke can be extrapolated to PAD.

The key question is whether these perceptions about PAD (eg, PAD does not lead to mortality) are accurate or not. A body of evidence has been indicating that PAD is strongly associated with mortality, primarily as a strong predictor of future myocardial infarction and stroke. Moreover, limb-related complications attributable to PAD, such as lower extremity amputation and acute limb ischemia (ALI), are devastating. Also, the causes of PAD and the other atherosclerosis diseases are not identical, despite considerable overlap, indicating the need for specific diagnostic and treatment approaches for PAD. To help clinicians grasp the contemporary epidemiology of PAD and the major gaps in the management of PAD, a working group with expertise in cardiology, general internal medicine, geriatrics, epidemiology, vascular surgery, and vascular medicine has compiled this scientific statement.

DEFINITION OF PAD

Historically, the terms peripheral artery (or arterial) disease and peripheral vascular disease have been used loosely.[4] These terminologies have often included any or all atherosclerotic disease separate from cardiac disease, including carotid artery, renal artery, leg artery, and aortic diseases.[5] Peripheral vascular disease may additionally include peripheral venous and lymphatic disease. In an era of precision medicine, we believe that precise definitions should be used.[6] For the purpose of this scientific statement, we define PAD as “lower extremity PAD.” Specifically, we are referring to atherosclerotic obstruction from the aortoiliac segments to the pedal arteries.

AWARENESS

Despite its high prevalence and the morbid and mortal outcomes detailed later in this statement, overall awareness regarding PAD is limited. In the PARTNERS study (Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival) conducted in primary care practices throughout the United States in 1999, among patients with a prior PAD diagnosis, 83% of patients, yet only 49% of their physicians, were aware of the PAD diagnosis.[2] Even in a recent systematic review of PAD knowledge and awareness, 61% of general practitioners reported screening patients for PAD, whereas only 6% were aware of guidance regarding evidence-based therapies for PAD.[7] In this same study, the results of formal examinations of medical students and trainee physicians demonstrated poor to modest overall knowledge regarding PAD-related data gathering and its interpretation. Among patients and the general public, PAD awareness ranged from 21% to 61%. Lack

of patient and health care professional awareness contributes to delayed or underused treatment, as detailed later in this statement.

Multiple factors likely contribute to this lack of PAD awareness. First, as noted earlier, there has been variability in the nomenclature and definition of PAD, which presents a challenge to effective communication about the disease. Second, variation in the clinical presentation of PAD is also likely a source of confusion regarding PAD.[5,8] Only 10% to 30% have typical intermittent claudication (ie, exertional calf pain resolving within 10 minutes of rest), with the remaining having either no exertional leg symptoms (20%–50%) or atypical leg symptoms (40%–50%).[2] Atypical leg symptoms may include pain/discomfort that begins at rest or pain/discomfort that does not cause the patient to stop walking, pain/discomfort that does not consistently resolve with rest[1]; these symptoms can be confused with symptoms of lower extremity arthritis or degenerative spinal disease. Last, an important component of PAD unawareness is the lack of knowledge and appreciation among health care professionals and patients of the poor prognosis of PAD. In this context, the terminology of "peripheral" in PAD may provide an impression that this clinical condition is not critical.[10] However, as noted later in this statement, this notion is clearly incorrect, because PAD is associated with various adverse outcomes. Thus, increasing awareness of all aspects of PAD, including the definition, diagnosis, clinical manifestation, and complications, is critical to improving overall outcomes among this growing and undertreated population.

PREVALENCE AND TEMPORAL TRENDS

Overall PAD

PAD is the third leading cause of atherosclerotic morbidity, following coronary heart disease and stroke. A systematic review of 34 studies (22 from high-income countries and 12 from low- and middle-income countries) demonstrated that the prevalence of PAD was ≈5% at 40 to 44 years of age and ≈12% at 70 to 74 years of age in both men and women in high-income countries (Figure 1).[11] The prevalence of PAD in women in low- and middle-income countries was very similar to that in high-income countries, but the corresponding estimates for men in low- and middle-income countries compared with high-income countries were ≈2% and ≈8%, respectively. Between the years 2000 and 2010, the number of persons living with PAD increased by 13.1% in high-income countries and 28.7% in low- and middle-income countries.

Another recent systematic review estimated that 238 million people were living with PAD in 2015: 64 million living in high-income countries and 172 million living in low- and middle-income countries.[12] Thus, PAD should be recognized as an increasingly global problem. A recent publication from the Global Burden of Disease study also indicates that PAD cases have risen each year since 1990.[13] Similarly, disability-adjusted life-years, years of life lost, and years lived with disability increased over this period. These changes represent population growth rather than a change in age-specific incidence. Worldwide, the age-specific prevalence has been largely steady.

The prevalence of PAD in the United States at ≥40 years of age is estimated to be ≈7%, corresponding to 8.5 million adults, from a study pooling 7 community-based studies.[14]

However, these studies were conducted in the late 1990s or in the beginning of 2000. For example, the National Health and Nutrition Examination Survey, a nationally representative cohort, has not measured ABI since 2004. Especially given the obesity and diabetes epidemic,[15] a contemporary estimate of PAD prevalence in the United States is needed.

Critical Limb Ischemia/Amputation

Critical limb ischemia (CLI) (or chronic limb-threatening ischemia[16]) is a severe form of PAD and usually defined as PAD with rest pain, nonhealing wounds, or tissue loss.[1,17] A systematic review has reported that the 1-year cumulative incidence for each of mortality and amputation is ≈20% among patients with CLI.[18] Because few population-based studies have investigated CLI, the epidemiology of CLI is not well understood. Using data from the Marketscan database, which includes medical records from large employers' health plans, Medicare, and Medicaid, Nehler et al[19] reported that the prevalence of CLI is 1.3%, accounting for 11% of diagnosed PAD cases, among the eligible study population ≥40 years of age. The rate of CLI admission in the United States was constant between 2003 and 2011, with ≈150 per 100 000 population.[20]

The rate of lower extremity amputation declined from 2000 to 2009, but since has started to increase in people with diabetes.[21] Specifically, the total annual amputation rate per 1000 individuals with diabetes was 3 in 2009 but exceeded 4.5 in 2015. Although the exact reasons behind this increase in lower extremity amputation in diabetes are unclear, it is important to note that the increase was consistently observed in both major (above ankle) and minor (below ankle) amputations. In the same period, the annual amputation rate in people without diabetes was constant at ≈0.17 per 1000 individuals.

Lifetime Risk

Lifetime risk estimate is a useful parameter to communicate long-term risk, especially among younger adults whose 10-year risk estimate is low and thus cannot inform long-term decision-making of preventive therapies. The American Heart Association (AHA) and the American College of Cardiology (ACC) 2018 Guideline on the Management of Blood Cholesterol provides a lifetime risk algorithm for people 20 to 59 years of age but does not take into account PAD.[22] In this regard, a recent US study estimated lifetime risk of PAD by pooling 6 community-based US cohorts.[23] According to that study, the lifetime risk of PAD was estimated to be ≈30% in Black men and women and ≈20% in White and Hispanic women and men. The study demonstrated that, for a given age, sex, and race/ethnicity, the lifetime risk estimate of PAD can vary by 3- to 5-fold depending on the status of the traditional risk factors for PAD such as smoking and diabetes. The calculator to predict lifetime risk of PAD is available online.[24]

DIAGNOSIS

Physiological Testing

ABI, the ratio of ankle-to-brachial systolic blood pressure, is the first-line noninvasive diagnostic method for PAD,[1,25] requiring standardized measurement methodology.[26] An ABI ≤0.90 is considered PAD.[1,25,26] The diagnostic performance of ABI to detect PAD, with

>50% stenosis based on imaging modalities as the gold standard, is reasonably good, with sensitivity and specificity, respectively, at 61% to 73% and 83% to 96%.[27–29]

Several studies have shown that women tend to have lower ABIs than men, potentially because of shorter height.[30,31] A population-based study specifically explored this issue and found that, after accounting for demographic and clinical factors (eg, age and height), healthy women had on average an ABI 0.017 lower than healthy men.[32] Nonetheless, given the small difference from a clinical perspective for individual diagnosis, major clinical guidelines use the same ABI threshold of 0.90 in both sexes.[1,25]

The ABI can be falsely high in the presence of stiffened ankle arteries related to medial artery calcification, a condition mostly observed in patients with diabetes or chronic kidney disease (CKD).[33,34] In this scenario, it is recommended to measure the toe-brachial index (TBI), the ratio of the toe-to-brachial systolic blood pressure,[1,25,34] because medial calcification rarely affects digital arteries (detailed techniques to measure TBI can be found elsewhere[35]). In general, a TBI ≤0.70 is accepted as diagnostic for PAD.[1] A recent study including 1162 patients from a US vascular laboratory demonstrates that the overall accuracy (the proportion of tests that were either true positive or true negative) of the TBI to detect PAD was consistent in patients with diabetes versus those without diabetes (74% versus 78%). However, this was not the case for ABI, which had an accuracy of 66% in patients with diabetes versus 81% in patients without diabetes.[34] This study reported a similar pattern for CKD versus non-CKD. Of importance, a few studies have recently demonstrated that TBI may predict poor outcomes beyond ABI in patients with diabetes or CKD.[36–38] This evidence supports the simultaneous measurement of ABI and TBI in patients with diabetes or CKD for detecting PAD.

An ABI 0.90 to 1.0 is considered as borderline low ABI and cannot rule out PAD.[26] As detailed later in the statement, a body of evidence indicates that borderline low ABI is associated with increased risk of mortality and reduced physical function. In the case of borderline low ABI, particularly if symptoms suspect for exertional leg ischemia are present, the sensitivity to detect PAD can be improved by measuring ABI after a treadmill test (heel raise is an alternative method).[26] Although the criteria to evaluate postexercise ABI have not been standardized,[39] postexercise ABI <0.90 or a drop of ABI >20% or ankle pressure drop >30 mm Hg are usually considered as diagnostic.[26] Postexercise ABI should be also considered in patients with potential intermittent claudication with normal ABI.

Another option to overcome ABI limitations is to study the ankle arteries' Doppler flow pattern and velocities. In the San Diego Population Study, the addition of tibial artery Doppler assessment identified 20% additional diseased legs missed by the ABI.[40] Waveform analysis enables us to detect occlusive disease despite calcified arteries in patients with diabetes, and to identify those at high risk of cardiovascular disease (CVD) and limb events.[41]

Besides ABI and TBI, other physiological tests include segmental perfusion pressure and transcutaneous oxygen pressure. The former enables us to localize the pressure drop downstream of a significant stenosis, whereas the latter assesses the tissue oxygenation, not

only useful to quantify the consequence of malperfusion, but also to identify viable tissue after revascularization, and a *contrario* for delimitation of the amputation line in severe cases.[42]

Imaging

Noninvasive imaging for the assessment of anatomy and severity of arterial stenosis for patients with PAD has evolved over the past decade because of technical improvements.[42] These include the ability to image distal vessels with calcification, lower contrast dose, and higher spatial resolution. The selection of imaging modalities to diagnose PAD should depend on several factors, including the patients' symptoms (eg, claudication versus CLI), kidney function, and ABIs.

Computed Tomographic Angiography—Multidetector computed tomography scanners, including helical and multistation axial acquisitions, have now enabled the rapid scanning of the entire arterial system.[43] For evaluating the indication of revascularization in patients with PAD, both computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) are accepted as appropriate imaging tests.[44] The sensitivity and specificity of multidetector CTA compared with angiography is ≈90% for detecting PAD.[45] CTA uses iodinated contrast and ionizing radiation to visualize pathology from the aorta to the lower extremity. The scan times take a few seconds, but diagnosis can be difficult in small tibial vessels with calcification and multiple occlusions. The recent development of 256-row CTA has made detecting stenosis in the tibial location possible,[46] except in patients with calcified disease. New imaging techniques are being developed, including computed tomography perfusion to allow visualization of hypoxic regions of the lower extremity,[47,48] which can also demonstrate the effect of interventional treatment.[49,50]

Magnetic Resonance Angiography—The sensitivity and specificity of MRA in detecting PAD with stenosis >50% is the same as CTA, 90% to 100%.[51] MRA has several advantages in diagnosing PAD over CTA. MRA requires no radiation, calcium does not interfere with the diagnosis, and it can be helpful in evaluating for bone marrow edema in patients who have ulcers with possible osteomyelitis. However, the procedure time is considerably longer. Also, there is a concern of gadolinium-induced nephrogenic systemic fibrosis in patients with decreased kidney function. However, a recent systematic review including 4931 patients with a glomerular filtration rate <30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$showed that there were zero cases of nephrogenic systemic fibrosis when a group II gadolinium-based contrast agent (gadobenate dimeglumine, gadobutrol, gadoterate meglumine, or gadoteridol) was used.[52] Also, noncontrast MRA can be an option in some patients in capable facilities.[53] Another advantage of MRA is that it allows for hemodynamic measurements. Advanced techniques such as blood oxygenation level-dependent imaging and arterial spin labeling allow for assessing changes in perfusion to the calf muscle without gadolinium.[54,55]

Duplex Ultrasound—This modality is safe to all patients but is operator dependent. The sensitivity and specificity depend on several factors, including the presence of calcium in the arterial wall, the location or depth of the vessel, and the presence of multiple occlusions at different locations.[56] The femoral and popliteal arteries can usually be assessed

well, whereas the iliac vessels and aorta can be challenging because of the presence of bowel gas and body habitus. This modality can also take some time to perform a complete examination. Ultrasound is often used to assess the effectiveness and patency after endovascular and surgical treatment.[57] New advances using contrast-mediated ultrasound are being developed to evaluate perfusion to the lower extremity.[58]

Catheter-Based Angiography

Catheter-based angiography remains the gold standard for diagnosing PAD but is now limited to patients receiving endovascular revascularization.[1] New techniques are available that help to reduce the use of iodinated contrast, where CTA and MRA imaging can be fused to the angiogram, which has the potential to reduce the use of contrast and radiation.[59] Also, in some institutions, CO_2 angiography is used as a replacement or supplement (to reduce contrast) of conventional contrast-based angiography. Other new innovations to assess perfusion in CLI are discussed in a separate AHA scientific statement.[42]

SCREENING

In 2018, the US Preventive Services Task Force stated that the evidence regarding a recommendation for screening for PAD among individuals without symptoms indicative of PAD as part of cardiovascular risk assessment was inconclusive.[60] On the other hand, some expert organizations, including the AHA, recommend screening of PAD with ABI in adults at high risk (eg, adults ≥65 years of age and those 50–64 years of age with traditional risk factors).[1,61] A recent Danish trial[20] demonstrated that the comprehensive screening of PAD (using ABI), hypertension, and abdominal aortic aneurysm (using ultrasound) among men 65 to 74 years of age, followed by optimization of statin therapy, aspirin, blood pressure control, and surgical aneurysm repair, as appropriate, reduced mortality by 7% over 5 years of followup.[62] Accordingly, AHA, together with a few other organizations, urges a wider implementation of PAD screening with ABI in high-risk populations.[63]

PAD has been traditionally thought of as affecting men more than women.[64] However, more recent population-based studies show conflicting results about the association of sex with PAD.[65–67] Based on ABI measurements, women appear to have an equal or higher prevalence of PAD than men.[31,68] For example, a study pooling data from 6 US community-based cohorts estimated that the prevalence of PAD is 5.0% in men and 5.9% in women ≥40 years of age.[30] We should interpret these results in the context of ABI tending to be lower with shorter height.[31] Nonetheless, men present more frequently with claudication symptoms, whereas women have a higher prevalence of asymptomatic PAD or CLI.[65] Consistent with this notion, women with symptomatic PAD tend to have more femoropopliteal occlusive disease and multilevel disease than men based on angiographic imaging.[69,70]

There are significant race-based differences in the prevalence and incidence of PAD. The aforementioned study pooling 6 US cohorts reported that the prevalence of PAD was 11.6% in Black individuals and 5.5% in non-Hispanic White individuals.[30] This discrepancy persists after adjustment for traditional risk factors.[71] Black patients also tend to present with more severe disease than White patients and have a higher risk of

major amputation.[72,73] Although not specified in major clinical guidelines,[1] health care professionals should recognize the elevated risk of PAD in Black individuals. Also, we should try to understand the social constructs behind this observation better.

In this context, several socioeconomic factors are related to PAD. Adults with low household income, low education levels, and higher neighborhood deprivation have >2-fold increase in the risk of PAD even after adjustment for CVD risk factors.[74,75] These associations are consistent across races.[75] There are some observational data to suggest that the socioeconomic associations with PAD may be related to treatment differences with secondary preventative medications,[76] although further research into this concept is necessary.

Although the sex differences in PAD prevalence and severity can be ascribed, at least in part, to hormonal differences,[77] race differences are likely related to social determinants of health.[78] Disparities in access to care, mistrust of the medical system, and structural racism may contribute to reduced risk factor treatment, a delayed diagnosis of PAD, and, subsequently, a higher risk of major amputation in diverse populations.[79–82] Further research investigating structural inequities as a fundamental driver of health disparities, as recently called for by the AHA,[83] will be critical for better understanding racial inequities in the prevalence, incidence, treatment, and complications of PAD.

RISK FACTORS

Conventional Risk Factors

Evidence has supported traditional cardiovascular risk factors in PAD such as diabetes, smoking, dyslipidemia, and hypertension. A sedentary lifestyle also increases the risk in the development of PAD.[84] The Edinburg study reported that the risk of PAD is inversely related to physical activity.[85] Of these conventional risk factors, diabetes and smoking are particularly strongly related to the development of PAD.[86,87]

Individuals with diabetes are at an increased risk of developing asymptomatic or symptomatic PAD, with an increase in claudication of 2- to 3-fold greater compared with individuals without diabetes.[88–91] Diabetes worsens outcomes in patients with PAD, by mostly affecting infrapopliteal arteries, increasing risk of CLI, amputation, and mortality.[92–94] Accordingly, ≈70% of nontraumatic lower extremity amputations in the United States occur in patients with diabetes,[21] disproportionally to its overall prevalence of 12%.[95]

From another perspective, PAD is an important contributor to diabetes-related foot ulcer, a devastating condition with a high mortality risk and high medical cost affecting ≈13% of patients with diabetes in the United States.[96–98] Up to half of patients with diabetes-related foot ulcer have PAD.[99] The presence of PAD significantly worsens the prognosis in patients with diabetes-related foot ulcer with decreased healing rates, recurrence of ulceration, major limb amputation, and long-term survival.[100,101]

Like diabetes, cigarette smoking doubles the risk of PAD compared with nonsmoking.[102,103] The risk increases cumulatively with the number of cigarettes smoked and the start age of tobacco use, with starting before 16 years of age having the greatest risk.[104,105] Although smoking cessation decreases the risk of PAD, a recent community-based cohort study demonstrated that it takes up to 30 years for the risk for PAD of the individuals who stopped smoking to reach that of individuals who do not smoke, whereas the risk for coronary heart disease returns to the baseline within 20 years (Figure 2).[87]

Several studies have demonstrated total cholesterol and low levels of high-density lipoprotein cholesterol to be associated with PAD.[106,107] In addition, apolipoprotein B and lipoprotein(a) levels have been shown as independent risk factors.[108–110] A recent trial in patients with established CVD treated with hepatocyte-directed antisense oligonucleotide revealed a dose-dependent reduction of lipoprotein(a),[111] although the risk reduction of CVD including PAD is yet to be determined. A recent analysis from the Women's Health Study has reported that small low-density lipoprotein particle, rather than low-density lipoprotein cholesterol, was associated with incident PAD.[112] This study also has shown that triglyceride-rich lipoproteins may be especially important in the development of PAD. This observation has a clinical implication because icosapent ethyl, a triglyceride-lowering medication, has reduced major adverse cardiovascular events in REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial),[113] although this trial has not reported results for PAD as an outcome.

Evidence supports the robust association of elevated blood pressure with PAD.[106,114] The association is more evident for systolic blood pressure than diastolic blood pressure.[115] Specifically, in the ARIC study (Atherosclerosis Risk in Communities), systolic blood pressure demonstrated a graded association with PAD, with an adjusted hazard ratio of 2.6 at ≥140 mm Hg and 1.6 at 120 to 139 mm Hg, whereas the significantly elevated risk of PAD was only observed above 90 mm Hg for diastolic blood pressure.[115] This observation has clinical implications regarding how blood pressure should be interpreted for PAD risk.

Nonconventional Risk Factors

PAD develops as an inflammatory cascade within arterial walls leading to atherosclerosis. In the Edinburgh Artery Study, inflammatory markers such as CRP (Creactive protein) and IL-6 (interleukin-6) were found to be elevated in patients with symptomatic PAD.[109] Studies have found that elevated levels of these inflammatory markers are associated with the most severe form of PAD and at the highest risk for CVD events. Hemostatic factors such as fibrinogen have been associated as an independent risk factor[114] and a strong predictor for the development of PAD.[116,117]

Some studies suggest HIV as a risk factor for PAD.[118,119] A US study including veterans showed that individuals with a sustained CD4 cell count <200 cells/mm^3 had nearly 2-fold higher risk of PAD than individuals without HIV. There was no excess risk among individuals with a CD4 cell count ≥500 cells/mm^3.[118]

There is evidence demonstrating an association between metals and cardiovascular disease.[120–125] Despite mounting evidence, the relationship is underappreciated. For

instance, lead exposure has been shown to contribute to 10 times the number of cardiovascular deaths originally estimated.[120] The association of blood lead and PAD in National Health and Nutrition Examination Survey 1999 to 2000, revealed that blood lead levels were 14% higher in cases with PAD than without.[126] The Strong Heart Study evaluated the association of urine cadmium concentrations with the incidence of PAD, showing a prospective association between PAD and urine cadmium, independent from smoking.[127] Higher urine cadmium levels have been associated with an increase in PAD severity, with no PAD having the lowest urine cadmium concentration and CLI with the highest levels of urine cadmium.[128]

Air pollution exposure is linked with CVD, including PAD.[129–131] A population-based study of 18 000 individuals, associated urban living with a 2- to 3-fold increased risk of PAD compared with individuals living in rural areas.[132] Similarly, those living near major roadways demonstrated a decrease in ABI.[131]

Depression has emerged as a risk factor for the incidence and progression of PAD.[133,134] This may be attributable to medication noncompliance or a decrease in physical activity. The Heart and Soul study revealed a hazard ratio of 2.09 (95% CI, 1.09–4.00) of developing PAD in patients with depressive symptoms after adjustment for sex and age.[135] Individuals with depression and PAD had worse functional outcomes, greater need for revascularization, and worse quality of life.[136,137]

Microvascular Abnormalities

PAD is usually recognized as a manifestation of macrovascular disease. However, several recent studies have indicated the potential involvement of microvascular disease in the progression of PAD. For example, an international consortium of individual-level data including 0.8 million adults has shown that albuminuria, a representative measure of microvascular disease, is more strongly associated with leg amputation than overall PAD (eg, adjusted hazard ratio ≈6 versus ≈3 in urinary albumin-to-creatinine ratio >300 versus <10 mg/g).[138] Moreover, a community-based cohort has demonstrated that the presence of any retinopathy (eg, hemorrhage or exudates) was more strongly associated with the incidence of CLI and PAD than that of coronary heart disease or stroke (Figure 3).[139] Of importance, the association of retinopathy with PAD and CLI was independent of the duration of diabetes and hemoglobin A1c levels. Similar results have been shown in US veterans.[140]

These observations have important diagnostic and therapeutic implications. For example, the ABI, which reflects stenosis in relatively large arteries, may not be helpful to classify the risk of CLI or leg amputation in some patients. A small case series has reported wide distribution of ABI (ranging from 0.7 to 1.1) in patients with diabetes and CLI.[141] Of note, this study has demonstrated that all patients had TBI <0.7. Also, the current therapeutic options for patients with PAD (eg, statins and antiplatelets) are mainly based on evidence to prevent large artery disease or macrovascular disease (ie, coronary heart disease and stroke). Thus, future investigations on any therapeutic options targeting microvascular disease would be warranted.

COMPLICATIONS/COMORBIDITIES

Leg Symptoms, Physical Function, and Quality of Life

The magnitude and significance of functional impairment in PAD is underappreciated. Despite difficulty walking long distances, individuals with PAD frequently have atypical leg symptoms that can be mistaken for comorbidities such as hip or knee arthritis or spinal stenosis.[142] Some clinicians may attribute difficulty walking to normal aging. Some people with PAD report no exertional leg symptoms (ie, are asymptomatic) either because they have restricted their physical activity or slowed their walking speed to avoid ischemic leg symptoms.[142–144] Therefore, it is important for clinicians to suspect the possibility of PAD in people who report difficulty walking because of discomfort, weakness, cramping, or other symptoms in the hips, lower extremities, or feet. This is particularly the case if the symptoms resolve with rest and do not begin with rest and if the patient is >55 years of age with cardiovascular risk factors or a history of other cardiovascular disease. Cilostazol is the sole medication that the AHA/ACC PAD guideline recommends for ameliorating leg symptoms and improving walking distance in patients with PAD.[1]

The gradual but progressive nature of functional decline in PAD is also difficult for clinicians to detect without objective testing. Furthermore, patients with PAD who restrict their activity to avoid leg symptoms may not appreciate that their walking endurance has declined and may report stabilization of leg symptoms even as their 6-minute walk distance has declined.[145] A 6-minute walk test can be used to measure objective change in walking ability. Greater declines in 6-minute walk distance over time are associated with adverse outcomes, including mortality and mobility loss.[146]

Atherosclerotic obstructions in lower extremity arteries prevent delivery of oxygenated blood to lower extremity skeletal muscle during walking activity, and many people with PAD cannot walk >2 to 3 blocks without stopping to rest because of ischemic leg symptoms such as cramping, weakness, or pain. It is important for health care providers to acknowledge patterns of atypical symptoms in patients with PAD. For example, hip, buttock, and lower back pain that occur with walking and resolve with rest are common in people with PAD and are likely attributable to atherosclerotic disease in locations proximal to the femoral arteries.

Consistent with the phenomenon of walking-induced ischemia, people with PAD have lower physical activity levels, poorer walking endurance, slower walking velocity, and poorer balance than people without PAD.[142–144,147,148] More severe PAD is associated with lower physical activity levels and greater functional impairment.[147] In the Walking and Leg Circulation Study cohort of 460 participants with PAD and 240 without PAD, lower ABI was progressively associated with a higher odds ratio of stopping to rest during a 6-minute walk test (eg, 11.7 [95% CI, 4.9–27.7] in ABI <0.50 and 6.6 [95% CI, 3.1–14.1] in ABI 0.50 to <0.70 compared with participants with ABI 0.9–1.5).

People with asymptomatic PAD also have significantly poorer functional performance than those without PAD.[142,143,149] In 2 large observational studies of older community-dwelling men and women, ≈65% of those with an ABI <0.90 consistent with PAD were

asymptomatic (ie, reported no exertional leg symptoms).[143,149] Yet these individuals with asymptomatic PAD still had significantly slower walking velocity, lower physical activity, and poorer walking endurance than people without PAD who also report no exertional leg symptoms.[143,149] Of note, borderline low ABI 0.9 to 1.0 has also been independently associated with reduced physical function.[143,148]

In addition to poorer performance on objective assessments of functional performance, people with PAD report poorer quality of life than those without PAD. In the ARIC Study with 5115 older adults, lower ABI was independently associated with lower quality of life.[150] The association was more evident for physical domains than mental domains of quality of life. This pattern was consistently observed in other studies.[151,152] Nonetheless, in a study of 957 patients with PAD presenting to 16 specialty clinics in the United States, Netherlands, and Australia, 336 (35%) had significant mental health concerns consisting of depressive symptoms, anxiety, and stress.[153]

Despite the significant functional impairment and impaired quality of life, people with PAD have traditionally been considered to have a benign natural history with regard to lower extremity outcomes.[154–157] This is because relatively few people with PAD will develop CLI or require amputation.[154–157] The gradual decline in walking performance may be less perceptible to patients and to clinicians than acute events such as ALI, creating a false perception of a benign natural history of lower extremity PAD.

Cognitive Function

Vascular dementia is a leading cause of dementia in older adults.[158] Moreover, a growing body of evidence demonstrates that vascular dysfunction and its risk factors contribute to the pathophysiology of Alzheimer disease as well.[159] Thus, it is not surprising that several studies documented associations of PAD and its severity with cognitive impairment and dementia.[160–164] Cognitive deficits in individuals with PAD reveal patterns of neuropsychological impairment similar to individuals with a history of transient ischemic attack. In particular, 25% of patients with PAD scored in the bottom 5% of control groups on tests assessing attention and frontal lobe function.[165] Although cognitive impairment is usually not considered as a complication of PAD, future studies are needed to evaluate the impact of cognitive function on the clinical management and prognosis among patients with PAD.

Leg Outcomes (CLI/ALI, Leg Amputations)

Lower extremity major amputations (typically defined at the level of the ankle or above) and ALI are often considered major adverse limb events. Amputation is not simply a complication but an important treatment option to save lives and proximal limbs. The association of PAD with mortality and other cardiovascular outcomes like myocardial infarction and stroke has been extensively evaluated. However, few studies have quantified the association of PAD (versus no PAD) with severe leg outcomes, although several clinical studies are exploring those outcomes only among PAD patients. There are no validated models to identify patients with PAD who are likely to develop CLI or need amputation. To

the best of our knowledge, whether ABI is associated with future CLI or leg amputation in the general population has yet to be reported.

ALI is a vascular emergency requiring immediate treatment for limb salvage and has recently attracted attention as an important complication of PAD. ALI usually represents a rapid or sudden (eg, <2 weeks) decrease of leg perfusion causing pain, pulseless, pallor, sensory loss, or paralysis.[1] However, to efficiently establish evidence on ALI, the field needs to develop a standardized definition of ALI. Nonetheless, a secondary analysis of the EUCLID trial (Examining Use of Ticagrelor in Peripheral Artery Disease) has reported that a history of leg revascularization was the most potent predictor of ALI (hazard ratio, 4.7 [95% CI, 3.3–6.8]), whereas the second strongest predictor, atrial fibrillation, had a hazard ratio of 1.8 (95% CI, 1.1–3.2).[166]

Mortality and Cardiovascular Outcomes

The ABI Collaboration reported a robust association of a low (≤0.90) and high (>1.40) ABI with all-cause and cardiovascular mortality from a meta-analysis of 16 population-based cohort studies.[167] In persons with an ABI between 0.81 and 0.90, total mortality was doubled and in those with an ABI ≤0.70 it was quadrupled. In this study, borderline low ABI also demonstrated significantly elevated mortality. Multiple studies in diverse populations have demonstrated that persons with PAD have higher risk of other CVDs such as coronary heart disease, stroke, and abdominal aortic aneurysm.[1,135] Another study adds heart failure to these outcomes.[168] The elevated CVD risk has been shown to be only partially attributable to shared CVD risk factors, such that at any given level of CVD risk factors, PAD is independently related to future CVD events and mortality.[169] PAD has also been shown to be predictive of future CVD events even when adjusted for other markers of subclinical atherosclerosis.[170] As a result, the AHA/ACC 2018 lipid guideline lists low ABI ≤0.9 as a risk enhancer, to be considered for guiding lipid-lowering therapy on top of the predicted risk of atherosclerotic CVD based on the Pooled Cohort Equation.[22]

PAD recently gained attention in the context of polyvascular disease. This refers to a subset of patients with atherosclerotic involvement of multiple vascular beds, including PAD. In several trials assessing new lipid-lowering or antithrombotic therapies in the field of cardiovascular prevention such as the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk) and the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies), patients with polyvascular disease demonstrated higher risk than those without, which was translated into higher absolute risk reduction with these new treatments.[171,172] For example, in the FOURIER trial,[171] as anticipated, PAD plus myocardial infarction/stroke had the highest risk of major adverse cardiovascular events (CVD mortality, myocardial infarction, and stroke), with 2.5-year risk of 14.9% (Figure 4). It is notable that PAD without myocardial infarction/stroke had a higher risk of major adverse cardiovascular events (10.3%) than myocardial infarction/stroke without PAD (7.6%).

GAPS AND CHALLENGES IN PAD MANAGEMENT

Underutilization of Evidence-Based Preventive Therapy

The most recent AHA/ACC PAD guideline was developed in 2016[1] and lists antiplatelet therapy, statins, antihypertensive agents, glycemic control, and smoking cessation as the Class I (strong) and IIa (moderate) recommendations. Despite these evidence-based guideline recommendations, patients with PAD remain undertreated (Table 1). In an analysis of persons with PAD (defined by ABI ≤0.9) from the National Health and Nutrition Examination Survey, the use of aspirin, statins, and renin-angiotensin system inhibitors was only 35.8%, 30.5%, and 24.9%, respectively.[173] A more contemporary study of patients undergoing peripheral revascularization, a subgroup at heightened risk for cardiovascular and limb ischemic outcomes, reported use of aspirin, $P2Y_{12}$ inhibitor, and renin-angiotensin system inhibitors in 67.3%, 57.7%, and 47.6% of patients, respectively, at discharge.[174] In the latter analysis, only 61.7% of patients were discharged on a statin. Provider efforts to help patients with smoking cessation were examined among 1272 patients with PAD cared for in vascular specialty clinics followed in the PORTRAIT Registry (Patient-Centered Outcomes Related to Treatment Practices in Peripheral Arterial Disease: Investigating Trajectories).[176] In this study, 37.3% (n=474) were smoking actively at baseline. Of these, only 16% were referred to smoking cessation counseling, and 11% were prescribed pharmacological treatment. At 12 months, 72% of all individuals who smoked at baseline continued to smoke. The illustrated underutilization of preventive therapies may reflect the lack of clarity regarding prevention goals in PAD, because many trials have included PAD as a minority subgroup of broader atherosclerotic CVDs such as coronary heart disease and stroke. Nonetheless, these data clearly highlight the need for efforts to improve the use of evidence-based therapies in patients with PAD.

Underutilization of Supervised Exercise Therapy

Supervised exercise is first-line therapy to improve walking impairment in people with PAD.[1] Supervised treadmill exercise is the most thoroughly studied exercise therapy for people with PAD. More than 30 randomized clinical trials of supervised treadmill exercise in people with PAD involving >1400 participants have been completed. In 1 meta-analysis, mean improvement in treadmill walking distance was 180 meters and mean improvement in pain-free walking distance was 128 meters, compared with a nonexercise control group.[177] Supervised exercise also significantly and meaningfully improves 6-minute walk distance and health-related quality of life in people with PAD.[178–180] Several randomized trials have also demonstrated that arm and leg ergometry exercise, respectively, each significantly improve walking distance in people with PAD.[181]

In 2017, the Center for Medicare & Medicaid Services announced the coverage of supervised exercise for symptomatic patients with PAD.[181] The Center for Medicare & Medicaid Services covers 12 weeks of supervised exercise, conducted 3 times weekly at a physician's office.[182] However, recent evidence showed that most people with PAD do not participate in supervised exercise programs.[182] Of 135 vascular physicians across the United States, 54% reported that a facility for supervised exercise was not available to them and 49% reported that they had never referred a patient with PAD for supervised exercise.

Barriers to supervised exercise participation include lack of medical center-based exercise facilities, costs, and the burden of repeated medical center visits.[183]

Structured home-based walking exercise interventions receive Class IIa recommendations in the AHA/ACC 2016 PAD guideline and have the potential to overcome some barriers of supervised exercise programs. However, home-based walking exercise interventions have had mixed benefits for improving walking ability in people with PAD.[179,184–188,188a] Three randomized trials of home-based walking exercise significantly improved walking ability, measured by 6-minute walk distance and treadmill walking performance, compared with a control group that did not exercise. These effective interventions have required periodic visits to the medical center for in-person coaching and feedback. A 6-month home-based exercise intervention that included weekly on-site visits to the medical center while helping patients with PAD adhere to walking exercise at home improved the 6-minute walk distance by 52 meters relative to a control group.[186] In contrast, a 9-month randomized trial of home-based exercise that primarily relied on telephone calls, tapering to once per month did not show significant benefit compared with usual care.[185] Although home-based exercise interventions can significantly and meaningfully improve 6-minute walk distance, it is important to keep in mind that the most effective interventions have incorporated regular visits to the medical center. A recent randomized clinical trial of home-based exercise in 305 participants with PAD demonstrated that exercise at an intensity that induced ischemic leg symptoms, but not exercise conducted at a comfortable pace without ischemic leg symptoms, significantly improved walking performance.[188a]

Gaps and Challenges in Revascularization

Revascularization for Intermittent Claudication—Guidelines from the AHA/ACC[1] and the Society for Vascular Surgery[61] recommend best medical treatment as the first-line treatment for claudication, with revascularization reserved for only refractory cases. These recommendations are based on data showing that there is a relatively low likelihood of limb loss associated with mild PAD[189] and that long-term improvements in symptomatology may be limited.[190] For example, recent data from the Invasive Revascularization or Not in Intermittent Claudication trial demonstrated that, after 5 years of follow-up, revascularization for claudication lost any early benefit and did not result in long-term health-related quality of life compared with best medical therapy.[190] Despite guidelines recommending medical management as the first-line therapy for claudication, recent registry data from the Vascular Quality Initiative demonstrate that 27% of all open bypass procedures and even a higher percentage of endovascular interventions are performed for claudication.[191] It is possible that many of the patients undergoing revascularization for claudication experienced severe claudication symptoms and that conservative management failed. For instance, in the CLEVER study (Claudication: Exercise Versus Endoluminal Revascularization),[192] the revascularization group and the supervised exercise therapy group had better 18-month outcomes than optimal medical care alone. Quality improvement initiatives aimed at reducing unnecessary procedures are emerging to address outlier behavior in the overuse of invasive interventions for mild disease.[177,193] Higher-quality data about the benefits of revascularization for severe claudication symptoms are needed.

Percutaneous Revascularization—The impact of percutaneous intervention in CLI is a subject of emergent research and the focus of active investigation. In a large observational study, percutaneous intervention compared with surgical therapy was associated with reduced in-hospital mortality (2.34% versus 2.73%, $P<0.001$), length of stay (8.7 days versus 10.7 days, $P<0.001$), and cost of hospitalization ($31 679 versus $32 485, $P<0.001$) despite similar rates of major amputation (6.5% versus 5.7%, $P=0.75$).[20] Also, the increase in percutaneous leg revascularization has been related to a decline in leg amputation in the United States.[20] Although many observational studies have suggested the benefit of percutaneous intervention in decreased amputation rates and mortality, to date, only one trial has compared percutaneous intervention with medical or surgical therapy in patients with CLI (see the Surgical revascularization section).

Furthermore, most studies to date have failed to account for anatomic factors that may influence patient selection toward percutaneous versus surgical intervention. The Society for Vascular Surgery has developed 2 limb-staging classification schemes to allow for more objective comparison of revascularization outcomes. The Wound, Ischemia, and foot Infection (WIfI) stage[194] and the Global Anatomic Staging System (GLASS)[16] are 2 classification systems intended to permit more meaningful analysis of outcomes for various forms of therapy in heterogeneous populations with CLI and should be reported whenever possible in major comparative studies moving forward.

With the increased use of percutaneous intervention in PAD, restenosis has been a continual obstacle. A growing proportion of patients are undergoing lower extremity bypass for a prior failed percutaneous intervention, and these secondary revascularization procedures have been associated with inferior 1-year outcomes.[195] Although many devices lack comparative proof to support their use as a definite approach, multiple randomized studies of drug-eluting stent or drug-coated balloon show promising results for decreasing restenosis rates in the femoral-popliteal segment.[196–202] Among the current therapeutic options, the paclitaxel-eluting or paclitaxel-coated devices consistently show a significantly higher primary patency rate, better target lesion revascularization rate, and cost effectiveness.[203,204] Although a metaanalysis has reported an increase of mortality in patients receiving paclitaxel drug-coated balloon/drug-eluting stent DES compared with controls, there is some recent evidence against this finding.[205] Nonetheless, the continued use of these devices should be individualized, carefully balancing the risks and benefits.[170]

Surgical Revascularization—The majority of open surgery for lower extremity revascularization is performed for CLI.[206] Although lower extremity revascularization for PAD is becoming increasingly common in the United States, the rate of open surgery is stable or declining.[207–209] Approximately 40% of all lower extremity revascularization procedures performed in the United States are open bypass surgery (versus 60% endovascular) because of the lower morbidity associated with endovascular procedures.[210]

However, there is still substantial debate about the efficacy of open surgery versus endovascular interventions for the treatment of PAD. In the BASIL trial (Bypass versus Angioplasty in Severe Ischaemia of the Leg), which is the only randomized controlled trial on the topic to date, a bypass-first strategy had overall outcomes similar to an

angioplasty-first strategy.[211] However, there was a significant overall survival benefit and a trend toward a benefit for amputation-free survival associated with open surgery among patients who survived >2 years.[212] Since that trial concluded >15 years ago, there have been major advances in endovascular technology that are associated with better long-term outcomes at higher costs.[213,214] As a result, the efficacy of endovascular versus open surgery revascularization for PAD remains unknown. The BEST-CLI trial (Best Endovascular vs Best Surgical Therapy for Patients with Critical Limb Ischemia), which just completed enrollment, will hopefully clarify optimal therapies for CLI.[214] As noted earlier, the application of objective anatomic staging systems such as WIfI[194] or GLASS[16] are necessary to equalize clinical and anatomic factors in addition to baseline patient risk factors in clinical trials and observational studies moving forward.

SUMMARY

Lower extremity PAD is a global public health issue that has been systematically understudied and underappreciated. Table 2 summarizes major gaps in research, clinical practice, and implementation related to PAD that were covered in this scientific statement and should be filled. Health care professionals, researchers, expert organizations, health care organizations, government agencies, industry, and the community should collaborate to increase the awareness and understanding of PAD and improve the quality of PAD diagnosis, management, and prognosis.

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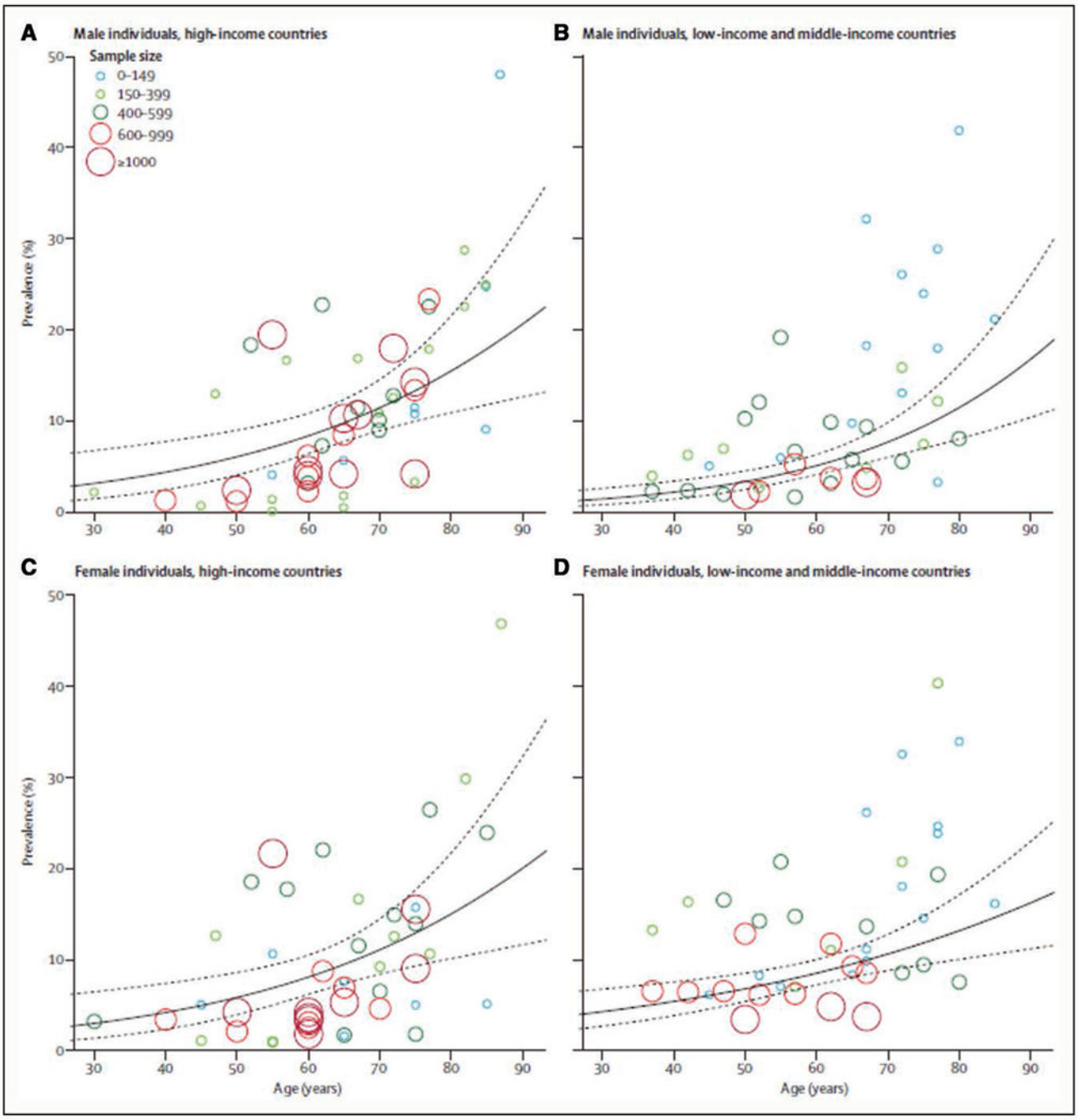

Figure 1. Prevalence of peripheral artery disease by age in men (A and B) and women (C and D) in high-income countries (A and C) and low- and middle-income countries (B and D).[11]
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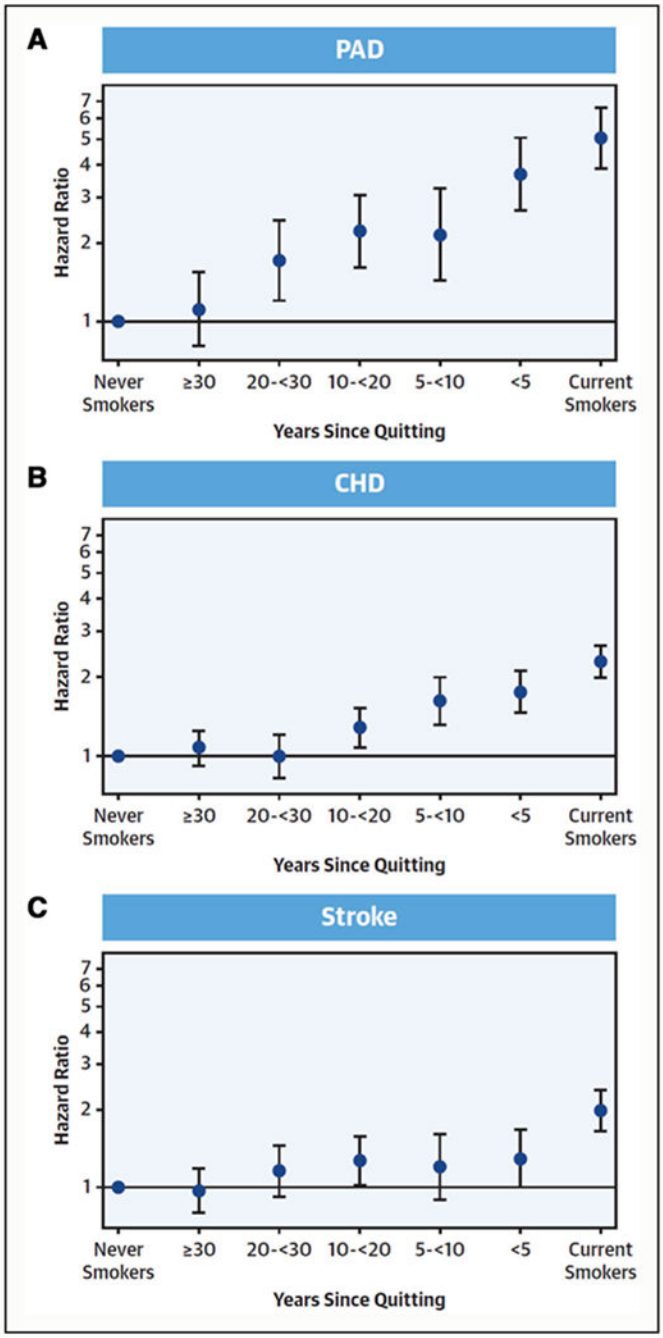

Figure 2. Adjusted hazard ratio of 3 major atherosclerotic diseases according to time since quitting smoking.[87]

A, Peripheral artery disease (PAD). **B**, Coronary heart disease (CHD). **C**, Stroke. Reprinted from Ding et al.[87] Copyright ©2019, with permission from the American College of Cardiology Foundation.

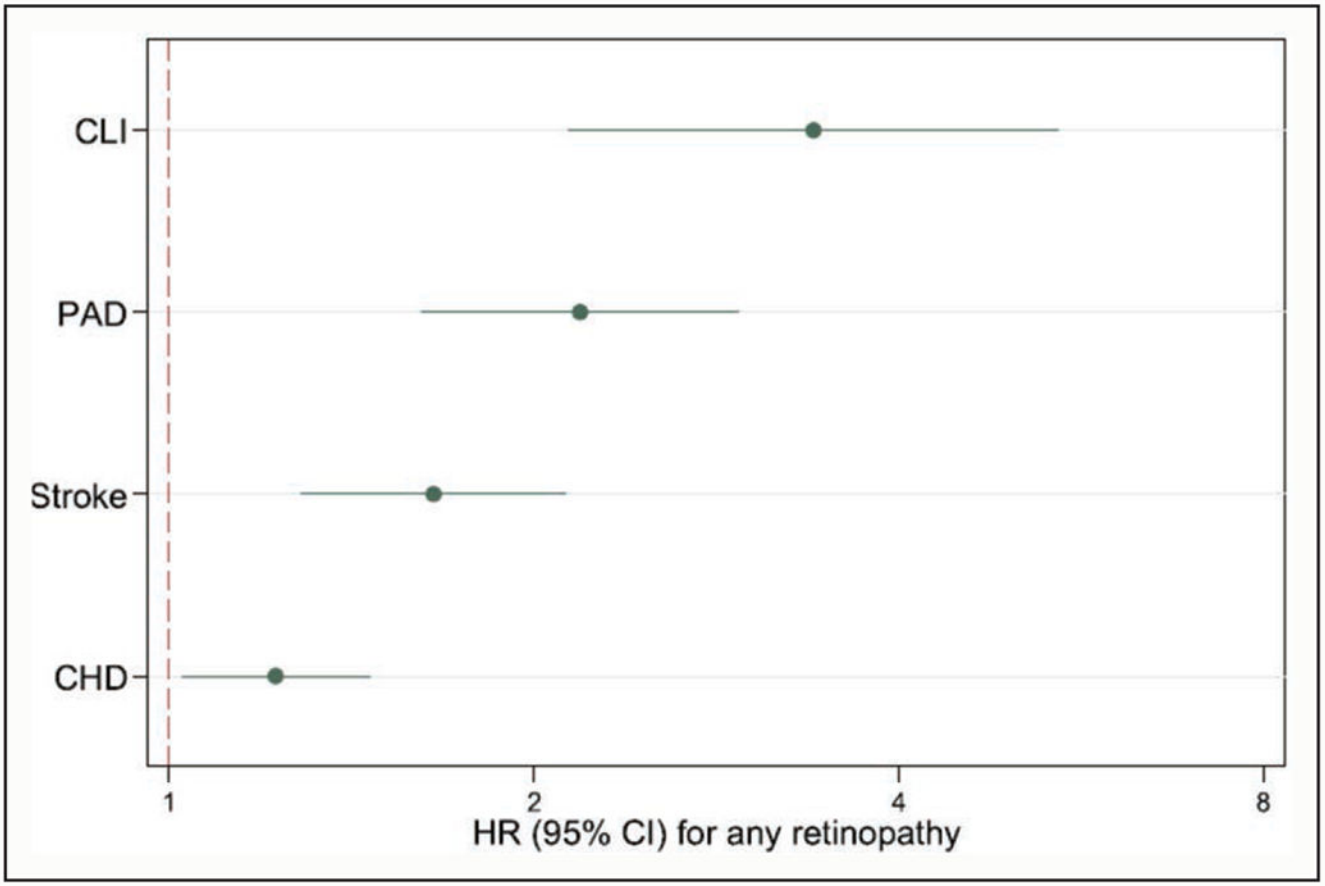

Figure 3. Hazard ratio (HR) of major atherosclerotic subtypes according to the presence versus absence of any retinopathy.[139]

CHD indicates coronary heart disease; CLI, critical limb ischemia; and PAD, peripheral artery disease.

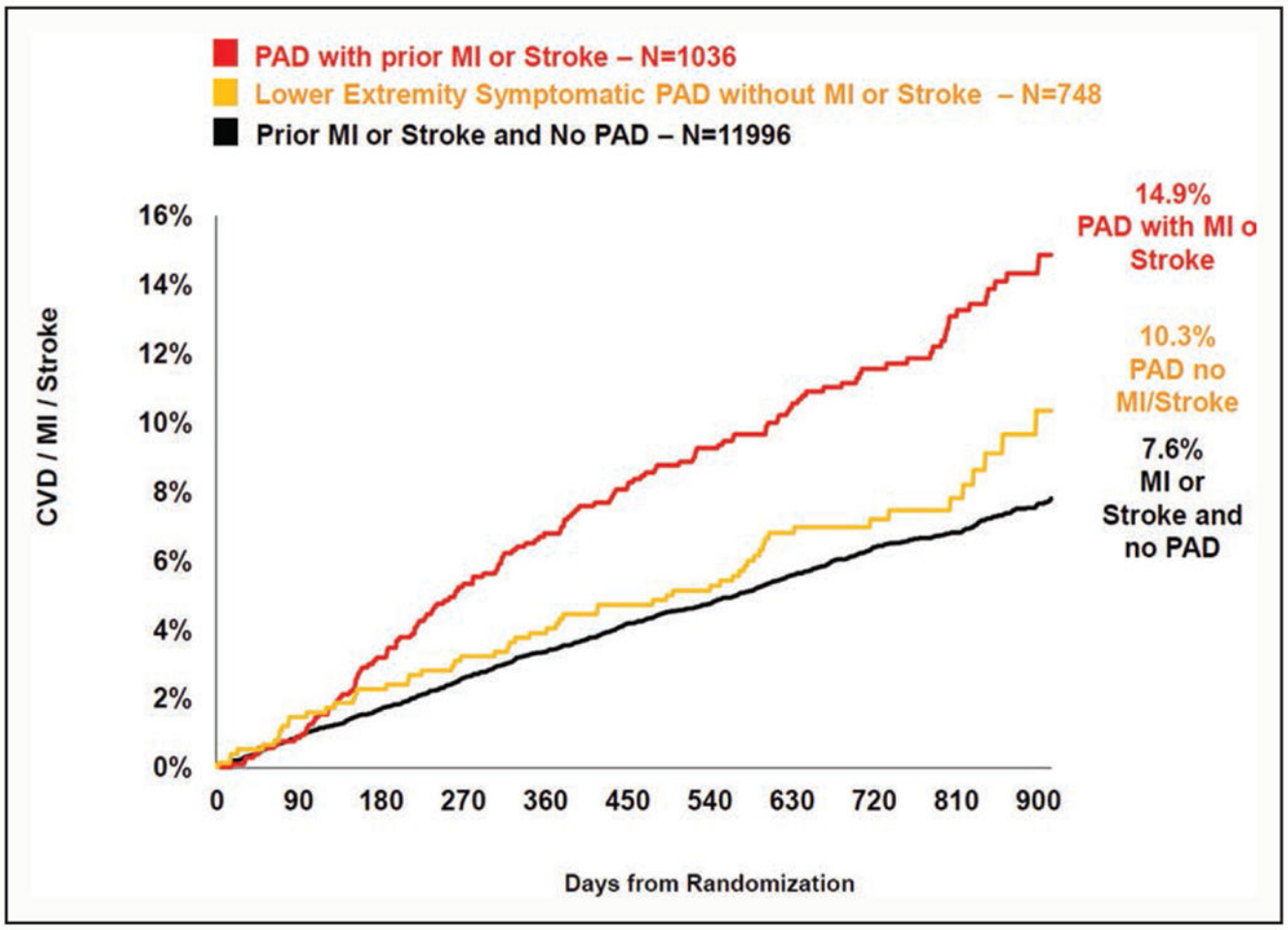

Figure 4. Cumulative incidence of major adverse cardiovascular events in the placebo group according to CVD status at baseline.[171]

CVD indicates cardiovascular disease; MI, myocardial infarction; and PAD, peripheral artery disease.

Table 1.

American Heart Association/American College of Cardiology 2016 PAD Guideline[1] Class I (Evidence Level A) Recommendations and Adherence in Patients With PAD

Class of recommendation	Level of recommendation	Recommendation	Adherence reported in literature
I	A	Aspirin or clopidogrel alone to reduce risk of myocardial infarction, stroke, and vascular death in patients with symptomatic PAD	57.7%–67.3%[173,174]
I	A	Statin therapy for all patients with PAD	30.5% (asymptomatic)[173] 61.7% (symptomatic)[174]
I	A	Antihypertensive therapy for all patients with hypertension and PAD to reduce risk of myocardial infarction, stroke, heart failure, and cardiovascular death	48%–60% use of angiotensin-converting enzyme inhibitor in symptomatic PAD[174,175]
I	A	Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit. Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (ie, varenicline, bupropion, and nicotine replacement therapy) or referral to a smoking cessation program	16% were referred to smoking cessation counseling. 11% received pharmacological treatment[176]

PAD indicates peripheral artery disease.

Table 2.

Summary of Gaps Related to PAD in Research, Clinical Practice, and Implementation

Research/clinical gaps
Contemporary data on the prevalence of PAD in the United States and globally
Larger studies with toe-brachial index (diagnostic accuracy and prognosis)
New and noninvasive techniques to visualize peripheral perfusion
Nonconventional risk factors and microvascular disease as potential preventive and therapeutic targets of PAD
Research to identify characteristics of effective home-based exercise interventions that are acceptable and accessible to patients with PAD
Behavioral methods to help patients with PAD adhere to home-based exercise long term
Community-based studies with severe leg outcomes
Randomized clinical trials comparing medical therapy, percutaneous revascularization, and surgical revascularization (with their latest evolutions) by indication and clinical staging
Medications or other oral therapies that significantly improve walking performance in PAD
Prediction models for developing critical limb ischemia and requiring lower extremity amputation
All PAD-related studies should include racially/ethnically diverse populations
Implementation gaps
Awareness of PAD among health care providers and patients
Screening of PAD with ankle-brachial index in high-risk populations
Broader use of toe-brachial index beyond ankle-brachial index>1.4, especially among patients with diabetes or chronic kidney disease
Adherence to evidence-based therapies in patients with PAD (medical therapies, supervised exercise therapy, and home-based exercise)
Avoiding unnecessary revascularization
All these implementation gaps should be filled across racially/ethnically diverse populations

PAD indicates peripheral artery disease.