Peripheral Artery Disease (PAD) is now the preferred term for partial or complete obstruction of ≥1 peripheral arteries. In this review, PAD refers to atherosclerotic occlusive disease of the lower extremities. Other terms used for this condition are peripheral vascular disease, peripheral arterial occlusive disease, and lower extremity arterial disease. Most of the existing literature on the epidemiology of PAD comes from highly developed countries. Recently, new information has been published from developing and developed countries. It is estimated that >200 million people have PAD worldwide, with a spectrum of symptoms from none to severe.

Symptom Assessment in PAD
It has been long recognized that an insufficient blood supply to the legs could cause pain and dysfunction in the same way that coronary artery disease could lead to angina. This type of pain...
is known as intermittent claudication (IC) and is characterized as leg pain associated with walking and relieved by rest. IC is generally indicative of exercise-induced ischemic leg pain, primarily in the calf, caused by PAD. Previous studies of PAD focused primarily on IC as a marker for PAD. Many patient questionnaires have been developed to identify IC and to distinguish it from other types of leg pain. The first of these was the Rose questionnaire, also referred to as the World Health Organization questionnaire. The San Diego Claudication Questionnaire is a modification of the Rose questionnaire that additionally captures information on the laterality of symptoms. A validated, shortened revision of the San Diego Claudication Questionnaire is shown in Table 1. Importantly, many people with PAD report no symptoms, including some patients with moderately severe disease. Reporting of leg pain can be influenced by factors other than PAD severity, such as the patient’s level of activity. In addition, many patients who do have ischemic pain have atypical symptoms, including pain reported as beginning at rest.4,5

### Ankle-Brachial Index

Because of the limitations of leg pain assessment, more objective measures are important. The measurement of blood pressure at the ankle was proposed as a test for PAD as early as 1950 and led to the development of the ankle-brachial index (ABI). The ABI is the ratio of the systolic blood pressure at the ankle to that in the arm. An abnormally low value of ABI is indicative of atherosclerosis in the legs. An ABI of ≤0.90 is commonly used in both clinical practice and epidemiological research to diagnose PAD, both symptomatic and asymptomatic. IC has been shown to have a low sensitivity but a high specificity for an abnormal ABI. For example, in the Rotterdam Study, 99.4% of subjects with an ABI of ≥0.9 did not have claudication; and among subjects with an ABI of <0.9 only 6.3% had claudication. In a study of elderly women in the United States, the percentages were 93.3% and 18.3%, respectively. Thus, PAD based on the ABI criteria is much more common than IC in the population. To validate the ABI, previous studies compared the ABI-based diagnosis with angiography, which was considered the gold standard for determination of atherosclerosis in the legs. Two such studies are often cited, in which the sensitivity and specificity of the ABI were shown to be in the 97% to 100% range.9,10 However, because angiography presents some risk to patients, it was not ethical to perform angiography on patients who were not suspected to have PAD. Therefore, these studies involved comparisons of patients with angiographically confirmed PAD with young, healthy patients assumed not to have PAD. The sensitivities and specificities calculated are therefore based on the ability of the ABI to discriminate between extremes of disease and wellness. If measured among patients seen in routine clinical practice or the population in general, the specificity of the ABI remains in the 97% range, but the sensitivity is lower, closer to 80%, in part due to some patients with PAD with stiff ankle arteries and false-negative ABIs.12 The ABI has also

<table>
<thead>
<tr>
<th>Table 1. San Diego Claudication Questionnaire, Brief Version</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Circle Answer</strong></td>
</tr>
<tr>
<td>1. Do you get pain or discomfort in either leg on walking? (if no, stop)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2. Does this pain ever begin when you are standing still or sitting?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>3. Does this pain include your calf/calves?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>4. Do you get it when you walk at an ordinary pace on the level?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>5. What do you do if you get it when you are walking?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>6. What happens to it if you stand still?</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Determine pain category separately for each leg as follows: (1) no pain: 1=no; (2) pain at rest: 1=yes and 2=yes; (3) noncalf: 1=yes, 2=no, and 3=no; (4) classic: 1=yes, 2=no, 3=yes, 4=yes, 5=stop or slow down, and 6=lessened or relieved; and (5) atypical calf: 1=yes, 2=no, and 3=yes and not classic.
been shown to have high intra- and inter-rater reliability.\textsuperscript{13} In practice, the ABI is measured using a blood pressure cuff, a standard sphygmomanometer, and a Doppler instrument to detect pulses. Technical considerations in measuring the ABI include the choice of ankle pressure for the ABI numerator and the choice of arm pressure for the ABI denominator. Many protocols have been suggested. In an attempt to provide the best evidence base for measuring the ABI, an international working group was assembled. The recommendations were published as an American Heart Association Scientific Statement in 2012.\textsuperscript{14} Selected key recommendations are summarized in Table 2. The recommendations are grouped into 5 categories: (1) measurement of ABI, (2) measurement of systolic pressures of the 4 limbs, (3) calculation of ABI, (4) use and interpretation of the ABI if clinical presentation of PAD, and (5) interpretation of ABI as a marker of subclinical cardiovascular disease (CVD) and risk in asymptomatic individuals. Within each of these 5 categories, specific issues concerning measurement and interpretation of the ABI are addressed.

As a diagnostic test for PAD, the ABI has several limitations. Occlusive disease distal to the ankle is not detected by the ABI; other measures, such as pressure ratios using pressures measured in the toe, are required for detecting such distal disease. The ABI is also sensitive to the patient’s height, with taller patients having slightly higher ABIs; it is unlikely that these differences are related to real differences in PAD.\textsuperscript{15,16}

In line with this, recent data document that in normal subjects, the influence of height on the ABI is small.\textsuperscript{17} On average, ABIs are slightly lower in women independent of height and slightly lower in African Americans (AA).\textsuperscript{17} This has little clinical effect on the diagnosis of PAD at an individual level but may contribute to an overestimation of PAD prevalence in population studies. Perhaps, the most significant limitation is arterial stiffness noted above. Recommendations for PAD assessment when the ABI is >1.40 are given in Table 2.

### Incidence and Prevalence of PAD

The study of PAD epidemiology raises many methodological issues that should be kept in mind while reviewing the literature. As discussed earlier, the definition of disease has evolved over time, with earlier studies focusing more on IC, as measured using Rose and other criteria, and later studies using the ABI, with a value of ≤0.90, now widely used to define disease. Uncommon among younger people, the prevalence of PAD rises sharply with age and affects a substantial proportion of the elderly population. Allison et al\textsuperscript{18} estimated the ethnic-specific prevalence in the United States combining data from 7 community-based studies. These studies included representation from 5 ethnic groups: non-Hispanic whites (NHW), AA, Hispanics, Asian Americans, and Native Americans. Evidence-based adjustments were used for studies that did not consider possible subclavian stenosis, previous revascularization for

<table>
<thead>
<tr>
<th>Steps</th>
<th>(1) Measurement of ABI</th>
<th>(2) Measurement of Systolic Pressures of the 4 Limbs</th>
<th>(3) Calculation of ABI</th>
<th>(4) Use and Interpretation of the ABI if Clinical Presentation of PAD</th>
<th>(5) Interpretation of ABI as a Marker of Subclinical CVD and Risk in Asymptomatic Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Doppler Method</td>
<td>Sequence of ABI at rest</td>
<td>For each leg: divide higher of the PT or BP pressure by higher of the right or left arm SBP</td>
<td>ABI used as a first-line noninvasive test for diagnosis of PAD</td>
<td>ABI provides incremental information beyond standard risk scores in predicting future CVD events</td>
</tr>
<tr>
<td></td>
<td>SBP in each arm</td>
<td>First arm</td>
<td></td>
<td>ABI≤0.90 is the threshold for confirming diagnosis of lower-extremity PAD</td>
<td>ABI≤0.90 or ≥1.40=increased risk of CVD events and mortality</td>
</tr>
<tr>
<td></td>
<td>SBP in each ankle</td>
<td>First PT artery</td>
<td></td>
<td>If ABI&gt;0.90 with clinical suspicion of PAD=use postexercise ABI or other noninvasive tests</td>
<td>ABI between 0.91 and 1.00 is borderline for CVD risk; further evaluation is appropriate</td>
</tr>
</tbody>
</table>
|       |                      | Other PT artery                               |                      | Postexercise ankle pressure decrease of >30 mm Hg or postexercise ABI decrease of >20%=diagnostic criteria for PAD | ...
|       |                      | Other DP artery                               |                      | If ABI=1.40 with clinical suspicion of PAD=use toe brachial index or other noninvasive tests | ...

\textsuperscript{1} Doppler Method

| 2     | Cuff size             | If the SBP of first arm is greater than SBP of other arm by at least 10 mm Hg, repeat BP of first arm and disregard first measurement | As a diagnostic tool for patients with PAD symptoms, each leg is reported separately | ...
|       | Width at least        |                      |                      | ...
|       | 40% of limb circumference |                      |                      | ...
|       |                      |                      |                      | ...

| 3     | Ankle cuff placement  | As a prognostic marker for CVD, use lower of the left and right ABIs (exception: noncompressible arteries) | If ABI>0.90 with clinical suspicion of PAD=use postexercise ABI or other noninvasive tests | ...
|       | Just above the malleoli |                      |                      | ...
|       | Straight wrapping method |                      |                      | ...
|       |                      |                      |                      | ...

| 4     | Open lesions covered with impermeable dressing | When ABI between 0.80 and 1.00, it is reasonable to repeat the measurement | Postexercise ankle pressure decrease of >30 mm Hg or postexercise ABI decrease of >20%=diagnostic criteria for PAD | ...
|       |                      |                      |                      | ...

**Table 2. Consensus Recommendations on ABI Measurement**

\textsuperscript{1} ABI indicates ankle-brachial index; BP, blood pressure; CVD, cardiovascular disease; DP, dorsalis pedis; MI, myocardial infarction; and PAD, peripheral artery disease; PT, posterior tibial; and SBP, systolic blood pressure.
PAD, or both. The results for men are shown in Figure 1. PAD was uncommon before the age of 50 years. Rates rose sharply with age, such that by the age of 80, rates were in the 20% range. Strikingly, the rate for AA was about twice that of NHW at any given age. Rates for Hispanics, Asian Americans, and Native Americans were similar for those in NHW. Figure 2 shows the data for women and reveals similar trends, although Native Americans have a rate nearly as high as AA. However, the data for Native-American women are limited and come from a single study, the Strong Heart Study. Overall, rates were similar for men and women. Worldwide, high-income developed countries report similar rates, although somewhat higher rates have been reported from the Netherlands. Recently, global estimates of PAD prevalence were published. In general, men and women from low-income and middle-income countries have modestly lower PAD rates than those in high-income countries.

Estimates of PAD incidence are reported somewhat less frequently in the literature, with more data based on IC incidence than on the ABI. At age 60 years of age, annual IC incidence rates in men have varied from a low value of 0.2% in Iceland to a high value of 1.0% in Israel. Data from Framingham Study show IC annual incidence increasing from <0.4 per 1000 in men aged 35 to 45 years to 6 per 1000 in men aged 65+ years. In women, IC incidence was about half that in men, although rates in men and women were similar by the age 65 to 74 years. A higher incidence of 1.6% per year was reported among men and women aged 55 to 74 years in the Edinburgh Artery Study; however, this study did not apply strict Rose criteria for probable IC. In the Reykjavik Study, Ingolfsson et al used Poisson regression techniques to conclude that IC rates among Icelandic men dropped significantly between 1968 and 1986; among 50-year-old men, their estimate of the rate of IC dropped from 1.7 per 1000 per year in 1970 to 0.6 per 1000 per year in 1984, whereas in men aged 70 years, the rate of IC dropped from 6.0 to 2.0. The authors attributed this to decreased smoking and cholesterol levels.

There are few studies of PAD incidence based on ABI, given the time and resources required to periodically retest study subjects for incident disease. In the Limburg peripheral arterial occlusive disease (PAOD) Study, incidence rates for PAD were based on 2 ABI measurements of <0.95. Among men, annual incidence was 1.7 per 1000 at the age of 40 to 54 years; 1.5 per 1000 at the age of 55 to 64; and 17.8 per 1000 at the age of ≥65. Annual incidence in women was higher: 5.9, 9.1, and 22.9 per 1000, respectively, for the same age groups. Sex differences in the incidence and prevalence of PAD are less clear than those in other CVDs. IC incidence and prevalence have usually been found to be higher in men than in women. For example, in the Framingham Study, annual IC incidence for all ages combined was 7.1 per 1000 in men versus 3.6 per 1000 in women, for a male to female ratio of 1.97. In the Framingham Offspring Study, IC prevalence was 1.9% in men versus 0.8% in women (ratio, 2.38), whereas in the Rotterdam Study, it was 2.2% in men versus 1.2% in women (ratio, 1.83). However, the Edinburgh Artery Study and the Limburg PAOD Study found much lower male to female ratios of IC prevalence of 1.1 and 1.2, respectively. The case for an excess of disease among men is less clear for PAD diagnosed based on ABI. This is true even in those studies finding a clear male excess with respect to IC. For example, in the Framingham Offspring Study, PAD based on ABI was found in 3.9% of men and 3.3% of women, for a ratio of 1.18. In the Rotterdam Study, ABI-based PAD was actually lower in men than in women, with prevalence of 16.9% and 20.5% for a ratio of 0.82. The Limburg PAOD Study, which reported a low male to female ratio for IC, reported a similarly low ratio of 1.1 for ABI-based PAD. A population-based study from Southern Italy found prevalence of PAD based on an ABI of <0.90 to be similar in men and women, with male to female ratios by the age of 0.89 to 0.99. In the Cardiovascular Health Study (CHS), an ABI of <0.90 was somewhat more prevalent in men (13.8%) than in women (11.4%; ratio, 1.21), but the association of disease with sex was not significant after adjustment for age and CVD status. The greater male excess observed for symptomatic versus ABI-diagnosed disease seems to be related to severity of disease. A prevalence study in Southern California found that the excess of disease among men increased with the severity of PAD. A report from the Multi-Ethnic Study of Atherosclerosis (MESA) showed that PAD prevalence (ABI<0.90) was the same in men and women (3.7%), but borderline values of ABI (0.90–0.99) were much higher in women (10.6% versus 4.3%). Other explanations related to the discrepancies in the sex ratio between IC- and ABI-defined PAD might be related to more frequent

Figure 1. Ethnic-specific prevalence of peripheral arterial disease in men in the United States. AA indicates African Americans; AI, American Indians; AS, Asian Americans; HS, Hispanics; and NHW, non-Hispanic whites.

Figure 2. Ethnic-specific prevalence of peripheral arterial disease in women in the United States. AA indicates African Americans; AI, American Indians; AS, Asian Americans; HS, Hispanics; and NHW, non-Hispanic whites.
presentation of some patterns of atypical pain in women, as well as a modestly intrinsic lower ABI in women. In general, more severe disease as manifested by lower ABIs or symptomatic disease is more common in men. A recent study evaluated a large representative US sample of ≈12 million insured adults for PAD and critical limb ischemia incidence and prevalence based on insurance claims. From 2003 to 2008, the annual incidence of PAD was 2.35%, and for critical limb ischemia, it was 0.35%. The prevalence of PAD was 10.69%, and for critical limb ischemia, it was 1.33%.

Global data on trends in PAD prevalence between the years 2000 and 2010 were recently published. Over that period, the number of individuals with PAD increased by 28.7% in low-income and middle-income countries and by 13.1% in high-income countries.

**PAD Risk Factors**

The strongest epidemiological evidence for a causal relationship between disease and putative risk factors comes from studies of incident disease. Such studies usually involve the measurement of risk factors at a baseline examination, with subsequent tracking of incident disease among the subjects. Acute events, such as myocardial infarction and stroke, lend themselves to such study because the date of onset of disease is generally documented in the records of healthcare providers and recalled by subjects. Conversely, the onset of PAD as defined by ABI is often asymptomatic, and in any case, it is unlikely to be documented other than through periodic re-examination of all the subjects, which involves substantial time and expense. For that reason, many studies of PAD risk factors are based on cross-sectional associations, that is, the association between current disease status and current risk factor measurements. Although such studies are potentially informative, the reported associations cannot conclusively prove causation because it is not known whether the risk factor preceded the disease or vice versa. Caution should, therefore, be exercised in reviewing the results of such cross-sectional studies, particularly where reverse causation is plausible. For example, low physical activity might cause IC, but IC might just as plausibly cause low physical activity. It is necessary to adjust for multiple potential risk factors in a single statistical model to accurately estimate the unique contribution of any single risk factor because the potential risk factors for PAD are themselves interrelated in various ways. The estimates presented here are based on such multiple adjustments for all traditional PAD risk factors, except as noted. Null findings may indicate the lack of a real association but may also be based on insufficient sample size. Most of the null findings discussed below are based on the failure of the risk factor of interest to remain statistically significant in stepwise regression models. The following discussion of risk factors focuses on the results from 5 large epidemiological studies, which are referred to as index studies (Table 3). These studies each had >3000 subjects drawn from the general population and included both men and women. These studies are similar enough in their selection and manner of measuring risk factors, and in their statistical analyses, to allow reasonable comparisons for most of the common risk factors. Table 3 also includes 11 other large studies, Although the discussion draws on data from many other studies, data are presented from these 5 index studies across all the conventional CVD risk factors to provide some consistency and comparability for the reader. The effect of age and sex on PAD incidence and prevalence is discussed above.

**Cigarette Smoking**

Smoking is one of the strongest risk factors for PAD in virtually all studies. Studies vary as to the measurement of smoking, often combining a categorical assessment of smoking status (current, past, or never) with some measures of current or historical volume of smoking, such as pack-years. However, even with some type of additional adjustment for volume of smoking, current smoking versus nonsmoking has been shown to at least double the odds of PAD in most studies, with some estimates as high as a 4× greater risk among smokers than others. Among the index studies, current smoking (versus never or former/never) resulted in 1.9 to 3.4× higher odds of PAD in the 3 studies using such categorization; however, in 2 of these studies, the models also included pack-years of smoking as a significant variable (Table 4). All of the large, population-based studies that were reviewed found a significant, independent association between PAD and smoking. According to recent data on incident cases of clinical PAD in US male professionals, smoking is the most contributive risk factor for occurrence of PAD, with a population attributable fraction of 44%. Cessation of smoking among patients with IC has been shown to improve various functional and physiological measures related to PAD, as well as reducing mortality. However, because symptomatic patients with PAD have long been advised to quit smoking, it is possible that observational comparisons of patients who quit smoking with those who do not are confounded by other differences in compliance with medical advice between the 2 groups. Randomized trials of this question would raise ethical issues. However, substantial bias is unlikely given the large effect size for cigarette smoking. In the Health Professionals Follow-up Study (HPFS), smoking was associated with increased risk of incident clinical PAD even after 20 years of smoking cessation, although this association was substantially diminished beyond 10 years after quitting smoking cigarettes.

There are limited data on the association of passive smoking and PAD. In a Chinese study conducted with women who have never smoked, the hazard ratio (HR) for PAD (either IC or ABI<0.90) after secondhand smoke exposure was significant at 1.67, with a significant dose–response relationship, both for the amount and the duration of exposure.

Similar relationships were reported from 2 studies of never smokers in Scotland. The first study used reported secondhand smoke as the exposure variable, whereas the second used salivary cotinine measures. Smoking seems to have an even more prominent role in PAD than in other atherosclerotic diseases. In a comparison of risk factors conducted in the same large cohort, Fowkes et al found smoking to be associated with a significantly higher relative risk for PAD compared with other CVDs; smoking was the only traditional CVD risk factor for which the odds ratio differed significantly between PAD and other CVDs.
Diabetes Mellitus

Diabetes mellitus is strongly associated with an elevated risk of PAD. Four of the 5 index studies found diabetes mellitus, dichotomized based on different criteria, to be associated with PAD after multivariable adjustment, with odds ratios ranging from 1.89 to 4.05.28,32–34 However, the Framingham Offspring Study found such an association on an age- and sex-adjusted basis but not in multivariable models.26 Despite its strong association with PAD but because of its lower prevalence in populations when compared with other traditional risk factors, the population attributable fraction of type-2 diabetes mellitus for incident PAD was estimated at 14% in a longitudinal study on US professionals.42 Among other large, population-based studies, multivariable logistic regression models have often shown a relationship with diabetes mellitus as a categorical variable19,22,25,37,40 or various blood sugar measures as linear variables.48

More severe or longstanding diabetes mellitus seems to be more strongly related to PAD. In the Hoorn Study, it was shown that known diabetes mellitus was associated with PAD in multivariable analysis, whereas newly diagnosed diabetes mellitus was only of borderline significance, and impaired glucose tolerance was not associated with PAD.19 However, one study in subjects aged >65 years reported a significant association between the homeostasis model assessment and PAD.47

Table 3. Studies of Peripheral Artery Disease in Populations

<table>
<thead>
<tr>
<th>Study Name</th>
<th>First Author, Year*</th>
<th>No. of Subjects</th>
<th>Country</th>
<th>Population</th>
<th>Study Design</th>
<th>PAD End point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Health Study</td>
<td>Newman, 1993</td>
<td>5084</td>
<td>United States</td>
<td>Aged 65+</td>
<td>Cross-sectional</td>
<td>ABI&lt;0.9</td>
</tr>
<tr>
<td>Framingham Study</td>
<td>Murabito, 1997</td>
<td>5209</td>
<td>United States</td>
<td></td>
<td>Cross-sectional</td>
<td>IC</td>
</tr>
<tr>
<td>Rotterdam Study</td>
<td>Meijer, 2000</td>
<td>6450</td>
<td>Netherlands</td>
<td></td>
<td>Cross-sectional</td>
<td>ABI&lt;0.9 (&lt;0.7 also studied)</td>
</tr>
<tr>
<td>Framingham Offspring Study</td>
<td>Murabito, 2002</td>
<td>3313</td>
<td>United States</td>
<td></td>
<td>Longitudinal</td>
<td>ABI&lt;0.9</td>
</tr>
<tr>
<td>Multi-ethnic Study of Atherosclerosis</td>
<td>Allison, 2006</td>
<td>6653</td>
<td>United States</td>
<td></td>
<td>Cross-sectional</td>
<td>ABI&lt;0.9</td>
</tr>
<tr>
<td>Other large studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quebec Cardiovascular Study</td>
<td>Dagenais, 1991</td>
<td>4570</td>
<td>Canada</td>
<td>Men only</td>
<td>Longitudinal</td>
<td>IC</td>
</tr>
<tr>
<td>Edinburgh Artery Study</td>
<td>Fowkes, 1992</td>
<td>1592</td>
<td>Scotland</td>
<td></td>
<td>Cross-sectional</td>
<td>ABI and reactive hyperemia</td>
</tr>
<tr>
<td>Israeli Ischemic Heart Disease</td>
<td>Bowlin, 1994</td>
<td>10059</td>
<td>Israel</td>
<td>Middle-aged men</td>
<td>Longitudinal</td>
<td>IC projected</td>
</tr>
<tr>
<td>Reykjavik Study</td>
<td>Ingolfsson, 1994</td>
<td>9141</td>
<td>Iceland</td>
<td>Men only</td>
<td>Longitudinal</td>
<td>IC</td>
</tr>
<tr>
<td>Honolulu Heart Program</td>
<td>Curb, 1996</td>
<td>3450</td>
<td>United States</td>
<td>Japanese American men</td>
<td>Cross-sectional and longitudinal</td>
<td>ABI&lt;0.9</td>
</tr>
<tr>
<td>Limburg PAOD Study</td>
<td>Hool, 2001</td>
<td>2327</td>
<td>Netherlands</td>
<td>Women aged 65+</td>
<td>Longitudinal</td>
<td>ABI&lt;0.95</td>
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<tr>
<td>Women’s Health and Aging Study</td>
<td>McDermott, 2000</td>
<td>930</td>
<td>United States</td>
<td>Women aged 65+</td>
<td>Longitudinal</td>
<td>ABI&lt;0.9</td>
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<tr>
<td>Physicians’ Health Study</td>
<td>Ridker, 2001</td>
<td>14916</td>
<td>United States</td>
<td>Male physicians</td>
<td>Nested case–control</td>
<td>IC or PAD surgery</td>
</tr>
<tr>
<td>San Diego Population Study</td>
<td>Criqui, 2005</td>
<td>2343</td>
<td>United States</td>
<td>Multi-ethnic</td>
<td>Cross-sectional</td>
<td>ABI&lt;0.9, abnormal waveform, PAD revascularization</td>
</tr>
<tr>
<td>National Health and Nutrition Examination Survey</td>
<td>Pande, 2011</td>
<td>7458</td>
<td>United States</td>
<td>Multi-ethnic American men and women aged 40+</td>
<td>Longitudinal</td>
<td>ABI&lt;0.9</td>
</tr>
<tr>
<td>Health Professionals Follow-Up Study</td>
<td>Joosten, 2012</td>
<td>51529</td>
<td>United States</td>
<td>Multi health professionals</td>
<td>Longitudinal</td>
<td>Clinical PAD†</td>
</tr>
</tbody>
</table>

ABI indicates ankle-brachial index; IC, intermittent claudication; PAD, peripheral artery disease; and PAOD, peripheral arterial occlusive disease.

*Where multiple articles were published, this refers to the article most frequently referenced herein.
†Includes limb amputation or revascularization, angiography with vascular obstruction ≥50%, ABI<0.9, or physician-diagnosed PAD.

Table 4. Cigarette Smoking and Peripheral Artery Disease

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Framingham Study</td>
<td>Per current pack/day</td>
<td>1.94</td>
<td>1.69</td>
</tr>
<tr>
<td>Framingham Offspring Study</td>
<td>Current smoker (vs. former or never)</td>
<td>2.00</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>Pack-years of smoking</td>
<td>1.03</td>
<td>1.02</td>
</tr>
<tr>
<td>Cardiovascular Health Study</td>
<td>Current smoker (vs. former or never)</td>
<td>2.55</td>
<td>1.76</td>
</tr>
<tr>
<td></td>
<td>Pack-years of smoking</td>
<td>1.01</td>
<td>1.01</td>
</tr>
<tr>
<td>Rotterdam Study</td>
<td>Current smoker (vs. never)</td>
<td>2.69</td>
<td>1.67</td>
</tr>
<tr>
<td></td>
<td>Former smoker (vs. never)</td>
<td>1.15</td>
<td>0.75</td>
</tr>
<tr>
<td>Multi-ethnic Study of Atherosclerosis</td>
<td>Current Smoker (vs. never)</td>
<td>3.42</td>
<td>2.48</td>
</tr>
</tbody>
</table>
incident PAD. Studies conducted in patients with diabetes mellitus have shown that duration of diabetes mellitus, level of glycemic control assessed by glycated-hemoglobin, and use of insulin are associated with PAD.

Outcomes of PAD in diabetic patients have been shown to be worse. In one study, diabetic patients with PAD were 5× more likely to have an amputation than other patients with PAD; they also had >3× the odds of mortality. There is also some evidence to support a somewhat different anatomic distribution of disease, with more disease in arteries distal to the knee in diabetic versus nondiabetic patients. Beyond ischemia, infection has an important role aggravating the risk of amputation in these patients.

Hypertension and Blood Pressure

The association of hypertension with PAD has been demonstrated in most studies in which blood pressure was studied. All 5 of the index studies reported a significant association between hypertension as a categorical variable and PAD. The lowest reported odds ratio was 1.32 as reported in the Rotterdam Study; this is somewhat understated relative to others, as it was based on a model that included both a categorical hypertension variable and an adjustment for systolic blood pressure level, which was also significant. Other than this, odds ratios for hypertension ranged from 1.50 to 2.20.

Most other large, population-based studies have also found a significant, independent association of hypertension or systolic blood pressures with PAD. Where both systolic and diastolic pressures were considered, systolic pressure was usually found to be associated with PAD, whereas diastolic pressure was not significantly associated. Although the relative risks associated with hypertension are modest in some studies, its high prevalence, particularly among older patients, makes it a significant contributor to the total burden of PAD in the population. For example, in one large study from the Netherlands, the odds ratio for hypertension was 1.32, but its attributable fraction (a measure of the proportion of PAD in the population attributable to hypertension) was 17.0%. In the Framingham Study, 30% of the risk of IC in the population was attributable to blood pressure in excess of 160/100 mm Hg. An even higher population risk attributable to hypertension, 41%, was recently reported in the HPFS. In these 3 latter studies, hypertension was second only to current smoking as the most contributive risk factor for PAD in population.

Dyslipidemia

In recent studies, the recognition that the total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio is the best lipid measure of risk, along with the increasing use of medication, has led to analyses that use both these variables in the same model or combine the ratio with medication use in a single variable, for example, dyslipidemia. Total cholesterol has been the most widely studied lipid measure as a potential risk factor for PAD. Total cholesterol was examined as a potential risk factor in 4 of the index studies, and it was significantly associated with PAD in multivariable analysis in 3; in the remaining study, total cholesterol was significant in univariable analysis but dropped out of multivariable models in which other lipid measures were considered. Similarly, in other studies, total cholesterol has usually been found to be associated with PAD with occasional null findings in multivariable analyses in which other lipid measures are considered. According to the HPFS, the population attributable fraction for PAD related to hypercholesterolemia is at 17%. HDL-C has been shown to be protective against PAD in most studies where it was evaluated, usually in models that also considered total cholesterol. HDL-C was included among the potential risk factors in 3 of the 5 index studies and the total cholesterol/HDL-C ratio in the fourth, and it was significantly associated with PAD in multivariable analysis in all 4. In 2 studies, both HDL-C and total cholesterol were significant in multivariable analysis, whereas in 1 study, HDL-C (but not total cholesterol) was significant. Other studies have also shown a protective effect of HDL-C. Bowlin et al found that non–HDL-C (total cholesterol minus HDL-C) was significantly associated with incident IC in a large cohort of Israeli men; neither total cholesterol nor HDL-C were significantly associated with disease in models that included non–HDL-C. In a comparison of incident cases of IC with healthy controls in the Physician’s Health Follow-up Study (PHFS), Ridker et al found that the ratio of total cholesterol/HDL-C was the lipid measure most strongly associated with disease, with patients in the highest quartile having 3.9× the IC risk of patients in the lowest quartile; screening for other lipid fractions was judged to have little clinical usefulness beyond measurement of this ratio. Previous case–control studies showed a consistent relationship between triglycerides and PAD, suggesting a uniquely strong relationship with PAD; however, large, population-based cohort studies using multivariable modeling later called this into question. Among the index studies, only 2 included triglycerides among the potential risk factors evaluated. In both cases, triglycerides were significant in univariable analysis but dropped out of multivariable models based on stepwise logistic regression. Similarly, in the Edinburgh Artery Study cohort and in a large study of geriatric patients in the United States, triglycerides were not significantly associated with PAD after adjustment for other lipid measures. However, other studies have shown triglycerides to be significantly and independently associated with PAD in multivariable analysis. There is also some evidence suggesting that elevated triglycerides may have a role in disease progression or more severe PAD.

In summary, although total cholesterol, HDL-C, and triglycerides all seem to be associated with PAD on a univariate basis, in multivariable analysis, triglycerides frequently drop out as an independent risk factor. It is unclear whether total cholesterol is the strongest independent risk factor for PAD; in one comparison of patients with PAD with healthy controls, it was found that mean total cholesterol did not differ significantly, whereas triglycerides, very low-density lipoprotein cholesterol, low-density lipoprotein cholesterol, HDL-C, and the total-cholesterol/HDL-cholesterol ratio all did. Total cholesterol and HDL-C seem to provide distinct information, and they lend themselves to summarization in a single ratio. Irrespective of results from multivariable analysis, simple descriptive statistics and clinical observation both suggest that patients with PAD are frequently diabetic or insulin resistant,
with the typical dyslipidemia of insulin resistance (ie, low HDL-C and high triglycerides).

Obesity
To date, the preponderance of evidence fails to support a consistent, independent positive association between obesity and PAD. In one of the few large studies with a positive finding, Bowlin et al estimated an odds ratio of 1.24 (95% confidence interval, 1.05–1.46) for incident claudication related to a 5.0-kg/m² difference in body mass index (BMI) in a study of 10059 Israeli men. Three of the index studies and many other large, population-based studies have failed to find a significant association between obesity and PAD or claudication after multivariable adjustment.21,25,26,33,34,60 There have also been many studies, including the other 2 index studies, in which higher relative weight or BMI was actually shown to be protective against PAD. In the Framingham Study, claudication was significantly inversely related to relative weight in men in multivariable analysis and seemed to have a U-shaped nonlinear relationship with relative weight in women.21 In an analysis from the Edinburgh Artery Study, BMI was significantly associated with less disease in preliminary multivariable analysis, although BMI was excluded from the article’s final multivariable model because it “suggested a counterintuitive effect.”36 The CHS found higher BMI to be significantly protective against PAD after multivariable adjustment in a large sample of Medicare beneficiaries.28 BMI was significantly protective against PAD (defined based on a combination of ABI, Doppler flow curves, and history of surgery) in the Hoorn Study.19 Similarly, the odds of PAD among subjects in the highest quintile of BMI compared with the lowest quintile were found to be significantly reduced in a cross-sectional analysis of elderly Japanese American men.37 Subjects with higher BMI were again shown to be at significantly lower risk of PAD in a study of Taiwanese subjects with diabetes mellitus.52 Finally, the multi-ethnic San Diego Population Study (SDPS) reported a significant inverse association of BMI and PAD.40

Obesity has been implicated in the causes of other risk factors for PAD, such as hypertension, type II diabetes mellitus, and dyslipidemia. In epidemiology, adjusting for factors that are on the causal pathway between a risk factor and disease is known to attenuate the observed strength of that risk factor. Therefore, estimates of risks related to obesity in multivariable models are estimates of the risk of obesity that artificially ignore most of the mechanisms by which obesity might reasonably cause PAD. In a few cases, unadjusted models or models adjusted only for age and sex show a significant association with PAD, although obesity was nonsignificant or protective after multivariable adjustment.26,36,60 However, in other studies, obesity was found to be either protective or non-significant even in unadjusted models or models adjusted only for age and sex.23,26,33,37,46 Thus, the failure to find more cases of positive association between PAD and obesity is not simply an artifact of adjusting for factors on the causal pathway in multivariable modeling.

Unaccounted for in the multivariable analyses just cited is possible residual confounding by cigarette smoking, which is strongly associated with both PAD and lower BMI. In addition, chronic illness in older patients, including PAD, may lead to weight loss, allowing for a spurious inverse correlation between obesity and PAD. Ix et al evaluated this question in the CHS of adults aged ≥65 years. In cross-sectional analysis, each 5-U increase in BMI was inversely associated with PAD (PR [prevalence ratio], 0.92). However, among people in good health who had never smoked, the direction of association was opposite (PR=1.20). Similar results were observed between BMI calculated using weight at the age of 50 years and PAD prevalence (prevalence ratio, 1.30), and between BMI at baseline and incident PAD events occurring during follow-up (HR, 1.32), among never smokers in good health. Thus, the reported inverse associations between BMI and PAD may be artifactual.

As in coronary artery disease epidemiology, there is some evidence to suggest that central adiposity may be more closely related to an increased risk of PAD. Vogt et al found that, after adjustment for BMI, higher waist/hip ratio was associated with significantly higher risk of PAD. In a group of patients with diabetes mellitus, it was shown that waist/hip ratio, but not BMI or body fat percentage, was associated with PAD.51

Alcohol Consumption
Evidence for a protective effect of light-to-moderate alcohol consumption, as seen in coronary heart disease (CHD), is less consistent for PAD. Two of the 5 index studies considered alcohol intake; neither showed alcohol to be significantly associated with PAD in either age- and sex-adjusted or multivariable models.26,33 However, in a later analysis of data from one of these studies, a significant protective effect was found in women but not in men.55 Conversely, a protective effect of alcohol was seen in men but not in women in the Edinburgh Artery Study, but this association disappeared after adjustment for social class.66 In Native Americans, a protective effect of alcohol was seen in multivariable analysis,57 but in elderly Japanese American men, alcohol intake was found to increase rather than decrease the risk of incident PAD.57 In a large Chinese population study, low alcohol intake was associated with decreased prevalence of PAD in men but not in women.58 Data from the PHF5 suggest that a protective effect related to moderate alcohol consumption may exist.59 In that study, there was no univariate association between alcohol and claudication incidence, but adjustment for cigarette smoking unmasked a significant protective association, reflecting the positive correlation of alcohol consumption with smoking, a strong risk factor for PAD.

Race and Ethnicity
Data on the association of race with PAD are limited because many of the large studies of PAD have been conducted in NHW groups. Several studies suggest a higher risk of PAD among blacks. A study conducted in elderly native Africans in 2 cities in Central Africa found high rates of PAD, 15% and 32%.70 The CHS, a study of 5084 Medicare beneficiaries in the United States, found that nonwhite (mostly black) race was associated with an odds ratio of 2.12 for PAD after adjustment for traditional risk factors.28 A study of 933 women aged ≥65 years found a higher percentage of black subjects among the PAD (36.3%) versus non-PAD (24.8%) groups.28 In the Atherosclerosis Risk in Communities (ARIC) study, Zheng et al found that PAD prevalence was higher in AA versus whites in both men (3.3% versus 2.3%) and women (4.0% versus 3.3%). The MESA
reported a multivariable odds ratio of 1.67 for blacks versus NHW. The SDPS reported an odds ratio of 2.34 for blacks versus NHW after adjustment for hypertension and diabetes mellitus, and additional analyses also showed no evidence of a greater sensitivity of blacks to traditional CVD risk factors. Finally, a synthesis of 3 studies addressing this question reported odds ratios of 2.3 to 3.1 for blacks versus NHW adjusted for age and sex; odds ratios of 1.7 to 2.9 after adjustment for traditional risk factors; and odds ratios of 1.5 to 2.0 after further adjustment for novel risk factors, including inflammatory risk factors. Thus, this association is in part explained by traditional risk factors and in part by novel risk factors, but there is an unexplained residual difference. Interestingly, hospital-based studies suggest that the anatomic distribution of disease may differ in blacks, with a higher percentage of distal disease in black subjects, even after adjustment for diabetes mellitus and other cardiovascular risk factors.

Data on other races and ethnic groups are more limited. A study of Native Americans suggested PAD prevalence comparable with that in NHW. In a study in Honolulu, Hawaii, Asians were reported to have lower PAD prevalence than comparable NHW subjects. Both the MESA and the SDPS data suggest somewhat lower rates of PAD in Asians and Hispanics compared with NHW. In a community-dwelling population aged >40 years living in Japan, a low prevalence of PAD (1.4%) has been reported.

Homocysteine

The association of homocysteine with PAD has been examined in many studies, with conflicting results. A 1995 meta-analysis of early case–control studies conducted in the late 1980s and early 1990s suggested an odds ratio of 6.8 for a 5-μmol/L difference in fasting total homocysteine (tHcy). To put this in perspective, the differences between the 25th and 75th percentiles of tHcy among controls in the Physician’s Health Study and a study of women in the Netherlands were between 3.5 and 4.0 mmol/L. The 5-μmol/L difference noted above is, therefore, not unreasonable as the difference between low and high tHcy levels in the population. In that light, an odds ratio of 6.8 might make homocysteine the single most powerful risk factor for PAD. Interestingly, the odds ratio for PAD in the meta-analysis was strikingly higher than odds ratios for coronary artery disease and cerebrovascular disease that were <2 in the same study.

However, more recent studies have produced much lower and frequently nonsignificant estimates of the PAD risk associated with homocysteine. In a large European case–control study, Graham et al estimated an odds ratio of 1.7 for subjects in the top quintile of tHcy for their control group versus all other subjects—a result of only borderline statistical significance. One population-based study from the Netherlands found an odds ratio of 1.44 for a 5-μmol/L difference in fasting tHcy, based on severe PAD involving surgery or an ABI of <0.5. However, an analysis of a subset of the Rotterdam Study cohort found no significant relationship between tHcy and PAD, based either on the conventional ABI cut-off of 0.9 or on an ABI cut-off of 0.7 for severe disease. The MESA reported a significant association for homocysteine after multivariable adjustment for traditional risk factors, but the association just missed significance after adjustment for other novel risk factors. A nested case–control study using the PHFS cohort failed to find any association between quartiles of fasting tHcy and IC. A case–control study of young women in the Netherlands also failed to find any significant association between fasting homocysteine and symptomatic PAD. More recently, 2 nested case–control studies within the Nurses Health Study and the HPFS cohorts found homocysteine levels positively associated and dietary folate intake inversely associated with risk of PAD in men but not in women. Among patients with PAD, disease progression based on ABI was not significantly different in patients with the highest and lowest 20% of homocysteine levels.

Although it is still possible that homocysteine may be an independent risk factor for PAD, it seems that the previous results summarized in the 1995 meta-analysis may have overstated the importance of homocysteine. Accordingly, a more recent meta-analysis of 14 studies in 2009 showed that homocysteine was significantly elevated (pooled mean difference, +4.31 μmol/L) in patients with PAD compared with controls. In the same article, the effect of folate supplementation on PAD was evaluated in 8 clinical trials and showed inconsistent findings.

C-Reactive Protein and Fibrinogen

C-reactive protein (CRP) and fibrinogen are 2 inflammatory markers that have been shown to be associated with PAD in many studies. In an analysis from the PHFS, each was found to be significantly associated with PAD in multivariable models, with odds ratios for the upper versus lower population percentiles of 2.2 for fibrinogen and 2.8 for CRP. However, these variables are highly correlated. Of the index studies, CRP was studied only in the MESA and it was not significant in multivariable analysis. However, fibrinogen was included in 4 of the 5 studies and was significantly associated with PAD in multivariable analysis in 3 of them. Other studies have also reported significant and independent associations of PAD with CRP and fibrinogen.

Chronic Kidney Disease

Several studies have shown an association between chronic kidney disease defined according to creatinine levels and PAD, particularly in the case of end-stage renal disease requiring dialysis. A recent article evaluated the markers of renal function in nested case–control studies in men and women. Microglobulin and cystatin C were both associated with incident PAD in men but not in women. Other studies reported poorer outcomes in patients with PAD in the case of concomitant chronic kidney disease, both in terms of limb loss and mortality.

Genetic Factors

Genetic factors seem to have a role in PAD, but data are limited. Wassel et al reported that in the SDPS, family history of PAD was independently and strongly associated with PAD prevalence and severity. This indicates a role for genetic factors or other shared environmental factors, or both, contributing to PAD. Similarly, in the Framingham Study, a family history of IC significantly predicted incident IC. In a study of fraternal and identical twins, Carmelli et al estimated that 48% of the variability in ABI could be explained by additive genetic effects. It has also been shown that familial
hypercholesterolemia, a genetic disorder, is related to a higher prevalence of PAD.\textsuperscript{95}

A meta-analysis of 21 genome-wide association studies in 41,692 people evaluated both categorical PAD (ABI $\leq 0.90$) and the continuous distribution of ABI as outcomes.\textsuperscript{96} One genome-wide significant association on chromosome 9p21, rs10757269, was identified for ABI. Two candidate genes for PAD and 1 single nucleotide polymorphism for coronary artery disease were associated with ABI, DAB2IP (rs13290547), CYBA (rs3794624), and rs1122608 (LDLR). No significant associations were found for categorical PAD. Using a categorical PAD definition, including revascularization, Kullo et al\textsuperscript{97} reported that in a genome-wide association studies, the single nucleotide polymorphism rs653178 in the ATXN2-SH2B3 locus was significantly associated with PAD. However, Wassel et al\textsuperscript{98} reported from the Candidate-Gene Association Resource consortium no strong genetic associations for either categorical PAD or the continuous measure of ABI. The genetic influence on PAD is an active area of investigation.

Other Risk Factors
A variety of other potential risk factors for PAD have been examined. In several studies, various measures of oral health have been shown to be independently associated with PAD.\textsuperscript{99} A study in young women found that self-reported history of various types of infectious diseases, such as chicken pox, shingles, mumps, pneumonia, chronic bronchitis, or peptic ulcer, was independently and significantly related to PAD.\textsuperscript{76}

Psychosocial factors were found to be associated with PAD in one large cohort in Scotland,\textsuperscript{100} whereas in a large study of Israeli men, anxiety, job-related stress, and manner of coping with job-related conflicts were all significantly related to incident IC even after adjustment for traditional risk factors.\textsuperscript{22}

Among patients with PAD, depressive symptoms were found to be associated with poorer lower extremity functioning.\textsuperscript{101}

Other possible risk factors for which some supporting data exist include antiphospholipid antibodies,\textsuperscript{102,103} hypothyroidism,\textsuperscript{104} sedentary lifestyle,\textsuperscript{105} and exposure to toxic heavy metals.\textsuperscript{106}

A PAD global burden in 2010 project compiled the data on PAD epidemiology and associated risk factors.\textsuperscript{2} Figure 3 presents the effect size of 11 risk factors investigated in at least 3 studies among those summarized in Table 3, using multivariate design, as well as the association with other CVD. These data suggest that globally cigarette smoking and diabetes mellitus are the strongest risk factors for PAD and also illustrate the strong overlap of PAD with other CVD (discussed below).

PAD Risk Scores
PAD risk scoring systems have been proposed, including a scoring system involving novel biomarkers not routinely

![Figure 3. Odds ratios for peripheral artery disease in high-income countries (HIC) and low- to middle-income countries (LMIC).\textsuperscript{7} BMI body mass index; CVD, cardiovascular disease, CRP, C-reactive protein; and HDL, high-density lipoprotein.](image)

![Figure 4. Prevalence and distribution of single-bed and polyvascular disease in REDuction of Atherothrombosis for Continued Health registry.\textsuperscript{129} CAD indicates coronary artery disease; CBVD, cerebrovascular disease; and PAD, peripheral artery disease.](image)
measured, but none has yet gained acceptance. Of note, the General Framingham score is used to predict a composite outcome of CHD, stroke, IC, or congestive heart failure. Analyses of prediction of the individual outcome components showed that an IC specific model and prediction of IC with the general score showed high concordance.

**Progression of PAD**
Little is known about the early natural history of PAD, particularly the progression from asymptomatic to early symptomatic disease. The average annual change in ABI has been estimated as −0.01 and −0.02 in various groups. However, these figures may be somewhat misleading because an average change in ABI masks a variety of changes of different directions and magnitudes.

A more meaningful approach may be to look at the percentage of the population achieving some categorically defined measure of change. The CHS, a population-based study, found that during 6 years of follow-up, 9.5% of people showed incident PAD, defined as an ABI drop of ≥0.15 to a level of ≤0.90. Nicoloff et al found that in 5 years, 37% of patients experienced a significant (≥0.15) worsening of ABI, whereas 22% of patients experienced clinical progression of PAD based on a change in symptoms or a need for surgical intervention. Among 415 English smokers with PAD referred for a surgical opinion, about one half experienced a significant (≥0.14) drop in ABI over the following 48 months. In a group of German patients with PAD, PAD was reported to progress in 18.6% of patients during an average follow-up of 64 months, based on a variety of criteria, including change in ABI. Bird et al defined a ranked series of 6 categories of PAD based on ABI and other tests; in a study of patients referred to a vascular laboratory, 30.2% of limbs progressed to a more serious category of PAD over an average follow-up time of 4.6 years.

In a study based on angiography, 9.1% of patients were found to have evidence of progression of PAD annually. In a study using development of rest pain or gangrene as the criteria for PAD progression, PAD progressed in 2.5% of patients annually. One study reported that PAD progressed at a rate of 3× greater in the first year after diagnosis than in subsequent years. Longer studies of PAD progression tend to be conservatively biased because people with faster progression are likely to have earlier mortality. Data on risk factors associated with progression of PAD are relatively sparse. In the CHS, significant independent predictors of decline were age, cigarette smoking, diabetes mellitus, and dyslipidemia. One report showed age, diabetes mellitus, classic IC, previous intervention, and PAD in the contralateral leg to be independently predictive of PAD progression. One study of English smokers with PAD identified hypertriglycerideremia as the most important independent risk factor for progression of PAD and onset of critical ischemia. Hemorheologic factors have been shown to be associated with an increased risk of need for vascular intervention. Patients with premature PAD (onset of symptoms at or before age 45) seem to have more rapid progression of disease and generally poorer outcomes. One study suggested that PAD progression in large arteries was related to smoking, the total cholesterol to HDL-C ratio, lipoprotein(a), and high-sensitivity CRP, but only diabetes mellitus was associated with progression in smaller arteries.

### Coprevalence of PAD and Other Atherosclerotic Disease
Given the common risk factors for PAD and other cardiovascular and cerebrovascular diseases, it is not surprising that people with PAD are more likely to have these other disorders concomitantly and vice versa (Figure 3, global data). Among 5084 Medicare beneficiaries in the CHS, the prevalence of history of myocardial infarction was 2.5× as high in subjects with PAD (based on ABI<0.9) versus those without; for angina, congestive heart failure, stroke, and transient ischemic attack, the prevalence rates were 1.9, 3.3, 3.1, and 2.5× as high, respectively. Conversely, the prevalence of PAD was 2.1× as high in patients with a history of myocardial infarction versus those without; the corresponding ratios for angina, congestive heart failure, stroke, and transient ischemic attack were 1.7, 2.6, 2.4, and 2.1, respectively. Other studies have found similar cross-sectional correlations. One study found correlations between the ABI and coronary artery disease severity estimated by the SYNTAX score. Subjects with PAD have also been shown to have an elevated prevalence of carotid artery stenosis, and a similarly modest but significant correlation between the severities of the 2 diseases has been demonstrated. The global REDuction of Atherothrombosis for Continued Health registry has highlighted the high prevalence of patients with PAD who also have concomitant coronary or cerebrovascular disease (Figure 4).

### PAD as a Predictor of Mortality and Morbidity
PAD is prospectively related to morbidity or mortality from other types of atherosclerotic disease, even after adjustment for known common risk factors. Although PAD seems unlikely to directly cause these other diseases, the presence of PAD may serve as a marker for underlying atherosclerotic processes or susceptibilities affecting other vascular beds. These prospective relationships are clinically important, to the extent that the PAD has prognostic value independent of other known risk factors.

Table 5 provides a summary of studies of the association of PAD with various mortality and morbidity outcomes. Table 5 is limited to studies using a noninvasive measure of PAD (usually ABI at various cut points). The clinical use of ABI testing is addressed. In addition, included studies required logistic or proportional hazards regression models, with multivariable adjustment for conventional cardiovascular risk factors. Results are shown with multivariable adjustment and after exclusion of subjects with baseline CVD where such exclusion was attempted.

Attempts to elucidate this association epidemiologically began with studies of patients having symptomatic PAD in the form of IC. Elevated mortality rates among subjects with IC were reported in the 1970s and 1980s in the Framingham cohort, although this excess risk was markedly attenuated when subjects with baseline cerebrovascular and CHD were excluded. Similarly, a Finnish study
### Table 5. PAD and Incident Cardiovascular Morbidity and Mortality

<table>
<thead>
<tr>
<th>Study</th>
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<th>Model Specifications</th>
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<td>Coronary heart disease mortality</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criqui, 1992&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Large-vessel PAD</td>
<td>4.3</td>
<td>1.4</td>
<td>12.8</td>
</tr>
<tr>
<td>Kornitzer, 1995&lt;sup&gt;134&lt;/sup&gt;</td>
<td>ABI&lt;0.9</td>
<td>3.6</td>
<td>1.1</td>
<td>11.8</td>
</tr>
<tr>
<td>Cardiovascular morbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newman, 1993&lt;sup&gt;131&lt;/sup&gt;</td>
<td>ABI&lt;0.9</td>
<td>2.1</td>
<td>1.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Hooi, 2002&lt;sup&gt;137&lt;/sup&gt;</td>
<td>ABI&lt;0.7 (vs. &gt;0.95)</td>
<td>1.7</td>
<td>1.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newman, 1999&lt;sup&gt;136&lt;/sup&gt;</td>
<td>ABI&lt;0.9</td>
<td>1.4</td>
<td>0.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Newman, 1999&lt;sup&gt;136&lt;/sup&gt;</td>
<td>ABI&lt;0.9</td>
<td>1.1</td>
<td>0.7</td>
<td>1.7</td>
</tr>
<tr>
<td>All coronary heart disease morbidity and mortality</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Ogren, 1993&lt;sup&gt;133&lt;/sup&gt;</td>
<td>ABI&lt;0.9</td>
<td>2.3</td>
<td>1.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Newman, 1999&lt;sup&gt;136&lt;/sup&gt;</td>
<td>ABI&lt;0.9</td>
<td>1.4</td>
<td>0.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Abbott, 2000&lt;sup&gt;141&lt;/sup&gt;</td>
<td>ABI&lt;0.8 (vs. &gt;1.0)</td>
<td>2.7</td>
<td>1.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Lee, 2004&lt;sup&gt;139&lt;/sup&gt;</td>
<td>ABI&lt;0.90</td>
<td>1.1</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Criqui, 2010&lt;sup&gt;142&lt;/sup&gt;</td>
<td>ABI&lt;1.0</td>
<td>1.8</td>
<td>1.3</td>
<td>2.7</td>
</tr>
<tr>
<td>&gt;1.4</td>
<td>2.2</td>
<td>1.1</td>
<td>4.2</td>
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<tr>
<td>All stroke morbidity and mortality</td>
<td></td>
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<tr>
<td>Newman, 1999&lt;sup&gt;136&lt;/sup&gt;</td>
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<td>1.1</td>
<td>0.7</td>
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<td>Abbott, 2000&lt;sup&gt;141&lt;/sup&gt;</td>
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<td>2.0</td>
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<td>3.5</td>
</tr>
<tr>
<td>Tsai, 2001&lt;sup&gt;143&lt;/sup&gt;</td>
<td>ABI&lt;0.9</td>
<td>1.4</td>
<td>0.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Hollander, 2003&lt;sup&gt;144&lt;/sup&gt;</td>
<td>ABI&lt;1.01 (vs. &gt;1.17)</td>
<td>1.3</td>
<td>0.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Murabito, 2003&lt;sup&gt;138&lt;/sup&gt;</td>
<td>ABI&lt;0.9</td>
<td>2.0</td>
<td>1.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Lee, 2004&lt;sup&gt;139&lt;/sup&gt;</td>
<td>ABI&lt;0.90</td>
<td>1.1</td>
<td>0.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Criqui, 2010&lt;sup&gt;142&lt;/sup&gt;</td>
<td>ABI&lt;1.0</td>
<td>1.6</td>
<td>0.9</td>
<td>3.0</td>
</tr>
<tr>
<td>ABI&gt;1.4</td>
<td>2.7</td>
<td>0.9</td>
<td>7.8</td>
<td></td>
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</tbody>
</table>

ABI indicates ankle-brachial index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; MI, myocardial infarction; and PAD, peripheral artery disease.
failed to find an association between IC and total or CVD mortality in men after adjustment for CVD risk factors and baseline CVD. Other studies demonstrated increased mortality risk among claudicants but did not fully adjust for the conventional CVD risk factors. However, in a large and methodologically rigorous study, data from the 18,403 men in the Whitehall cohort were used to show that after adjusting for CVD risk factors, IC was a significant predictor of CVD mortality, even after excluding subjects with baseline disease.

The development of the ABI and other noninvasive measures of PAD permitted further investigation of the association of PAD and CVD. In 1985, it was first demonstrated that a combination of noninvasive measures, including ABI, was prospectively related to all-cause mortality, even after adjustment for CVD risk factors and exclusion of subjects with baseline CVD. Relative risks in this study were in the range of 4 to 5; a later reanalysis of the same cohort with additional mortality follow-up demonstrated elevated relative risks for CVD and CHD in particular, with no significant increase in noncardiovascular death.

In the 1990s, many other prospective studies confirmed that ABI was related to CVD, based on either mortality or combined mortality and morbidity. This was found to be true in a variety of populations: vascular laboratory patients, an elderly patients with hypertension, elderly women, an employment-based cohort from Belgium, the Edinburgh Artery Study cohort, and the CHS cohort. Most of these studies controlled for various known CVD risk factors and the presence of CVD at baseline. The relative risks reported ranged from 2 to 5. Many of these studies also found PAD to be significantly associated with incident CHD in particular, although the CHS failed to find such associations for either total myocardial infarction or angina.

The data on the association of PAD with cerebrovascular disease are less conclusive. A 1991 study showed a strong association between multiple noninvasive measures of PAD and cerebrovascular disease morbidity and mortality, with risk ratios of 3.3 for men and 9.0 for women after multivariable adjustment. Data from the Edinburgh Artery Study also showed such an association based on ABI, although after multivariable adjustment, the association persisted for nonfatal but not fatal stroke. However, data from the CHS failed to show a relationship between low ABI and incident stroke. Another large study, the ARIC Study, showed a significant association between ABI and CVD as a continuous variable and ischemic stroke after multivariable adjustment but failed to show such an association when ABI was categorized based on a cut point of 0.80. The MESA reported associations with incident stroke for both low ABI (HR, 1.56) and high ABI (HR, 2.69), but both were of borderline significance because of modest numbers. Sutton-Tyrrell et al also reported elevated stroke risk in people with both low and high ABIs.

A meta-analysis of 16 population-based cohort studies evaluated the association of ABI with subsequent coronary events, CVD mortality, and total mortality. An ABI of ≤0.90 was associated with approximately twice the 10-year event rates in each of these 3 categories. In addition, these results held across the full range of Framingham Risk Score categories. The ABI was also evaluated as a continuous variable. As shown in Figure 5, there was a graded association of increasing risk with decreasing ABIs <1.00, with an HR of 4 for ABIs of ≤0.60. Risk was essentially flat for ABIs in the normal range, 1.00 to 1.40.

Population studies suggest that a high ABI, >1.40, is also associated with elevated risk of CVD. In the meta-analysis of 16 population studies, ABIs of >1.40 were associated with a modest but significant increase in total mortality, with an HR of 1.3. Such high ABIs are caused by stiff, often calcified ankle arteries, which may mask underlying PAD. Recently, the MESA reported that both low (<1.00) and high (>1.40) ABIs were associated with an increased risk of incident CVD events, even after adjustment for traditional and novel risk factors. Also, this was the first report

Figure 5. Hazard ratios for total mortality in men and women by ankle-brachial index (ABI) at baseline for all studies combined in the ABI collaboration.
to show that the ABI predicted events independent of other measures of extant atherosclerosis; specifically, coronary artery calcium, carotid intimal-medial thickness, and major ECG abnormalities. Evidence is contradictory as to whether the increased risk with a high ABI is restricted to people with underlying PAD. A vascular laboratory study from France in people with diabetes mellitus reported that increased risk of mortality for an ABI of ≥1.40 was restricted to people with underlying PAD. In contrast, a report from the Mayo Clinic vascular laboratory showed an independent risk for a high ABI that was further increased in the presence of underlying PAD. Further studies on this question are needed.

Recent evidence also indicates that, independent of baseline ABI, a more rapid deterioration in ABI carries a worse prognosis. Decreases in ABI of >0.15 were significantly associated with an increased risk of all-cause mortality (risk ratio, 2.4) and CVD mortality (risk ratio, 2.8) at 3 years, independent of baseline ABI and potential confounding variables. Through walking impairment and amputation, PAD is associated with significant disability worldwide. Data from the Global Burden of Disease projects in 1990 and 2010 show that along with mortality, disability associated with PAD has significantly increased, with this increase being greater among women than among men. In 2010, the disability-adjusted life years were the highest in Australasia, Western Europe, and North America, but the overall relative change in median disability-adjusted life years was larger in developing nations than in developed nations.

Summary and Conclusions

PAD is the atherosclerotic obstruction of the arteries of the lower extremities. The most common symptom of PAD is IC, which is pain in the legs associated with walking that is relieved by rest. However, noninvasive measures, such as the ABI, show that asymptomatic PAD is several times more common in the population than IC. PAD prevalence is sharply age-related, rising >10% among patients in their 60s and 70s. Prevalence seems to be higher among men than women for more severe or symptomatic disease. The major risk factors for PAD are similar to those for coronary and cerebrovascular disease, with some differences in the relative importance of factors. Smoking is a particularly strong risk factor for PAD, as is diabetes mellitus, and several newer risk markers have shown independent associations with PAD. PAD is associated with concomitant coronary and cerebrovascular disease. After adjustment for known CVD risk factors, PAD is associated with an increased risk of incident coronary and cerebrovascular disease morbidity and mortality. With the aging of the global population, it seems likely that PAD will be increasingly common in the future. The diagnosis and treatment of PAD in its asymptomatic stage may prove highly beneficial, particularly with respect to interventions aimed at ameliorating risk factors common to atherosclerotic disease of various vascular beds.

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Disclosures

Dr Aboyans declares modest conflict of interest with the following companies: AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Pfizer, and Sanofi. Dr Criqui reports no conflicts.

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In the Circulation Research article by Criqui and Aboyans (Epidemiology of Peripheral Artery Disease. Circ Res. 2015;116:1509–1526. DOI: 10.1161/CIRCRESAHA.116.303849.), corrections were needed.

In Figure 3, the label for the final risk factor, “Age (per 10 yrs),” was omitted.

In addition, the sentence describing the figure erroneously stated, “Figure 3 presents the meta-analyses of the effect size of 10 risk factors investigated in at least 3 studies among those summarized in Table 3, using multivariate design, as well as the association with other CVD.” It should read, “Figure 3 presents the meta-analyses of the effect size of 11 risk factors investigated in at least 3 studies among those summarized in Table 3, using multivariate design, as well as the association with other CVD.”

The authors apologize for these errors, and the errors have been noted and corrected in the online version of the article, which is available at http://circres.ahajournals.org/content/116/9/1509.full.