This chapter describes the epidemiology of peripheral artery disease (PAD). The definitions used to describe PAD and PAD syndromes are discussed. The prevalence and incidence, risk factors, progression and outcomes of PAD are summarized. Finally, the low awareness of PAD in the community is highlighted.

Definitions

Peripheral artery disease is an all-encompassing term used to describe disorders of the structure (including stenosis and aneurysms) and function of all non-coronary arteries [1]. Peripheral artery disorders include atherosclerosis, plaque rupture, abnormal vascular reactivity, vasospasm, inflammation, arterial wall dysplasia, and thrombus formation leading to occlusion. In the past, a range of other terms have been used, including peripheral vascular disease (PVD), peripheral artery occlusive disease (PAOD), lower extremity arterial disease (LEAD), and arteriosclerosis obliterans. The term “PVD” is not synonymous as it is less specific, potentially signify venous, arterial or lymphatic disease. PAD is preferred as it communicates the accurate anatomic disease site, is accepted in all current practice guidelines, and better communicates the disease site to patients and other health care professionals.

Lower extremity atherosclerotic PAD is a marker of systemic atherosclerosis which begins in childhood [2] as deposits of cholesterol and cholesterol esters called “fatty streaks” begin to line the intima of large and medium-sized arteries. At this stage, atherosclerosis is subclinical, but it can be quantified using arterial ultrasound imaging in other vascular beds (e.g., the extracranial carotid arteries) to measure carotid intima media thickness (cIMT). Various cohort
studies have demonstrated a higher prevalence of cardiovascular disease and increased incidence of poor cardiovascular outcomes in individuals with increased cIMT. This relationship of early atherosclerosis defined by cIMT measurements has been established in the Atherosclerosis in Communities (ARIC) study [3], the Osaka Follow-Up Study for Carotid Atherosclerosis 2 [4], the Cardiovascular Health Study (CHS) [5], the Rotterdam Study [6], the Tromsø study [7], and the Second Manifestations of ARTerial disease (SMART) study [8]. Progression of these fatty streaks by increased lipid accumulation, followed by development of a fibromuscular cap, lead to formation of a fibrous plaque. Risk factor exposure (e.g., smoking, diabetes, hypertension, diabetes, low high-density lipoprotein [HDL]-cholesterol concentrations, elevated non-HDL-cholesterol concentrations and obesity), lead to further progression of these atherosclerotic lesions and increase the risk of clinically manifest PAD and other atherosclerotic diseases [9]. Clinical PAD is detected when at least one infra-diaphragmatic stenosis leads to a measurable decrease in pedal systolic pressure measurements, with or without clinically recognized limb ischemic symptoms.

In this chapter, the term “PAD” is used exclusively to refer to partial or complete atherosclerotic obstruction of one or more lower extremity peripheral arteries.

### PAD Clinical Syndromes

There are five recognized clinical syndromes of PAD that are characterized by distinct presentations. These syndromes are useful both in describing the epidemiology of PAD and in clinical care. They include:

- asymptomatic PAD
- classic claudication
- atypical leg pain
- acute limb ischemia (ALI)
- critical limb ischemia (CLI).

Approximately one-half of individuals with PAD may be asymptomatic, defined by the absence of self-reported leg symptoms [10–14], and this has important implications in estimating the accurate PAD prevalence. PAD in these individuals is defined by a low (≤0.9) ankle–brachial index (ABI). The diagnosis of PAD is discussed in detail in Chapter 2. Claudication, which is the hallmark symptom of PAD, occurs in 10–35% [10–13] of individuals with PAD, and refers to the discomfort, pain, ache or fatigue in limb muscles that reproducibly occurs with exercise (e.g., walking) and is consistently relieved by rest [15]. Atypical leg pain is defined in individuals with objective evidence of PAD and who experience any leg symptom that is not classic claudication [16–18]. Up to
30–50% of individuals with PAD present with atypical pain [13, 15, 16]. ALI is defined by the clinical symptoms that arise with a sudden decrease in limb perfusion and that threatens the viability of the limb. While ALI is presumed to be an immediate vascular emergency, “acute” has been variably defined as occurring within 2 weeks of the initial ischemic presentation. ALI is usually due to thrombosis or embolism [19] and is clinically recognized by the “six Ps”: pain, paresthesia, pallor, pulselessness, poikilothermia, and paralysis. It is estimated that 0.1–1% of PAD patients may experience an episode of ALI [20, 21]. CLI manifests as chronic (>2 weeks) ischemic rest pain, non-healing ulcer or gangrene in 1–2% of PAD patients [22].

**Prevalence and Incidence**

There are an estimated 202 million people living with PAD globally, with almost 70% of them residing in low- and middle-income countries. Current data suggest that the global prevalence of PAD may be increasing, from 164 million individuals in the decade beginning in 2000–2010, representing an overall 23.5% rise in PAD prevalence (28.7% in low- to medium-income countries [LMICs] and 13.1% in high-income countries [HICs]) [23]. PAD affects most adult populations worldwide irrespective of socioeconomic or national developmental status [24, 25]. Fowkes et al. [23] recently collated the global prevalence of PAD using data from 34 studies (12 from LMICs and 22 from HICs). In women aged 45–89 years old, PAD prevalence ranged from 2.7% to 24.2% in HICs, and from 3.96% to 18.65% in LMICs. In men aged 45–89 years old, PAD prevalence ranged from 2.76% to 24.77% in HICs, and from 1.21% to 21.5% in LMICs.

Overall, PAD incidence and prevalence rates are similar in high- and low- to middle-income countries. PAD is as much a problem in HICs as it is in LMICs. Although the rates are similar, due to the greater population of people that live in LMICs compared with HICs, the number of individuals with PAD in LMICs exceed that in HICs (140.8 vs. 61.2 million people) (Figure 1.1). PAD is much more prevalent than common cardiovascular diseases, such as heart failure and atrial fibrillation [23, 26, 27] (Figure 1.2). Various studies have estimated the prevalence of PAD using the presence of claudication, identification of low ABI in asymptomatic individuals, or evidence of advanced forms of PAD (ALI or CLI). It is important to note that the prevalence of PAD in a given population depends on the characteristics of the population studied (i.e., age, ethnicity, socioeconomic status, and risk factors) and the method of diagnosis. In 2007, Allison et al. [28] summarized race- and ethnicity-specific estimates of PAD prevalence. They used data from seven community-based studies (the Cardiovascular Health Study, Honolulu Heart Program, Multiethnic Study of Atherosclerosis, US National Health and Nutrition Examination Survey, San
Diego PAD, San Diego Population Study and the Strong Heart Study). They found that with increasing age, the prevalence rates of PAD in men lay in the range 1.4–22.6% in non-Hispanic whites, 1.2–59% in blacks, 0.2–22.5% in Hispanics, 1.2–21.5% in Asians, and 2.6–28.7% in American Indians. PAD prevalence rates in women were in the range 1.9–18.2% in non-Hispanic whites, 3.0–65.1% in blacks, 0.3–18.2% in Hispanics, 0–18.2% in Asians, and 3.2–33.8% in American Indians. Eraso et al. [29] performed a multivariable age-, gender- and race/ethnicity-adjusted stratified analysis in this population, where the effect of each additional risk factor on the prevalence of PAD was

Figure 1.1 Prevalence of peripheral artery disease by age in men and women in high-income countries (HICs) and low- to middle-income countries (LMICs). Source: adapted from Fowkes et al. [23].
Prevalence and Incidence

measured. Non-Hispanic blacks (odds ratio [OR] = 14.7, 95% CI: 2.1–104.1) and women (OR = 18.6, 95% CI: 7.1–48.7) had the highest odds of PAD as a result of this cumulative effect (Figure 1.3).

Due to the time and resources required to periodically retest study subjects for incident disease, fewer studies have evaluated the incidence of PAD. In 1970, Kannel et al. [30] assessed claudication incidence in the Framingham study. They reported the age-specific annual incidence of claudication for ages 30 to 44 years as 6/10 000 in men and 3/10 000 in women. The incidence increased among those aged 65–74 years to 61/10 000 in men and 54/10 000 in women. In 1988, the Edinburgh Artery Study used detection of claudication determined by the World Health Organization (WHO) questionnaire, the ABI, and a hyperemia test, among individuals aged 55–74 years, and reported an incidence of 15.5/1000 person-years. Hooi et al. [31] studied the incidence of asymptomatic PAD among 2327 Dutch subjects defined by an ABI < 0.9. After 7.2 years, the overall incidence rate for asymptomatic PAD was 9.9/1000 person-years. More recently, using data from CHS, Kennedy et al. [32] found that during 6 years of follow-up, incident PAD was detected in 9.5% of the cohort as defined by an ABI decrease of > 0.15 to a level of ≤ 0.90. Table 1.1 summarizes the available data on the age- and sex-specific incidences of PAD.

There have been significant methodological challenges relating to measuring the sex-based incidence of PAD. The male:female ratio of incident PAD is higher when measured based on claudication alone, with one study reporting a ratio as high as 1.97. However, in studies that have used an ABI definition of PAD, the incidence rates are lower for men (0.8) or similar between men and women (Table 1.1). Prevalent claudication is also more common in men than in women, with male:female ratio ranging from 1.2 to 2.38. However, when ABI
Figure 1.3 Ethnic-specific prevalence of peripheral arterial disease: (a) men; (b) women. AA, African American; AI, American Indian; AS, Asian American; HS, Hispanic; NHW, non-Hispanic white. Source: adapted with permission from Allison et al. [28].
Table 1.1  Age- and sex-specific incidence rates of peripheral artery disease measured by claudication and ankle–brachial index (ABI).

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Mode of diagnosis</th>
<th>Age (years)</th>
<th>Men</th>
<th>Women</th>
<th>Male:female</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingolfsson et al. [33]</td>
<td>Iceland</td>
<td>Claudication</td>
<td>60</td>
<td>0.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowlin et al. [34]</td>
<td>Israel</td>
<td>Claudication</td>
<td>60</td>
<td></td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kannel and McGee [35]</td>
<td>US</td>
<td>Claudication</td>
<td>35–45</td>
<td>0.4/1000</td>
<td>0.2/1000</td>
<td></td>
<td>1.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥65</td>
<td>6/1000</td>
<td>6/1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Overall</td>
<td>7.1/1000</td>
<td>3.6/1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leng and Fowkes [36]</td>
<td>Scotland</td>
<td>Claudication</td>
<td>55–74</td>
<td></td>
<td></td>
<td></td>
<td>1.6%</td>
</tr>
<tr>
<td>Hooi et al. [31]</td>
<td>Netherlands</td>
<td>ABI &lt; 0.95</td>
<td>40–54</td>
<td>1.7/1000</td>
<td>5.9/1000</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>55–64</td>
<td>1.5/1000</td>
<td>9.1/1000</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥65</td>
<td>17.8/1000</td>
<td>22.9/1000</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Nehler et al. [37]</td>
<td>US</td>
<td>ABI &lt; 0.9**</td>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td>2.35%</td>
</tr>
</tbody>
</table>
is used in PAD diagnosis, the overall prevalence is similar in both sexes, with a male:female ratio range of 0.8–1.2. The Multi-Ethnic Study of Atherosclerosis (MESA) [38] found that although the prevalence of PAD defined by a low ABI was similar in both sexes, borderline ABI (0.9–0.99) was much more common in women than in men (10.6% vs. 4.3%). Further, McDermott et al. [39] reported that atypical leg pain is more common in women. Fowkes et al. [23], in the global PAD report, found that male sex had an odds ratio of 1.43 for PAD in HICs and 0.5 for low-to-medium income countries. The global OR was 0.83. Although it is likely that overall PAD prevalence is similar in both sexes, men are more likely than women to have more classic claudication symptoms, while women are more likely to have borderline ABI, asymptomatic PAD and atypical symptoms [40].

Tables 1.1 and 1.2 summarize the available data on the worldwide prevalence and incidence of PAD based on the method of diagnosis.

### Asymptomatic PAD

Asymptomatic PAD is defined as the presence of an ABI ≤ 0.9 without a clinically evident walking impairment or other leg symptoms. The ABI is performed

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Age (years)</th>
<th>Prevalence of ABI abnormalities (%)</th>
<th>Prevalence of IC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reunanen et al. [15]</td>
<td>5738 men</td>
<td>30–59</td>
<td>–</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>5224 women</td>
<td></td>
<td>–</td>
<td>1.8</td>
</tr>
<tr>
<td>Schroll and Munck [41]</td>
<td>360 men</td>
<td>60</td>
<td>16</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>306 women</td>
<td></td>
<td>13</td>
<td>1.3</td>
</tr>
<tr>
<td>Newman et al. [42]</td>
<td>82 men</td>
<td>&gt;60 (mean 72)</td>
<td>26.7</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>105 women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fowkes et al. [12]</td>
<td>809 men</td>
<td>55–74</td>
<td>24.6</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>783 women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newman et al. [42]</td>
<td>2214 men</td>
<td>65–85</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2870 women</td>
<td></td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Zheng et al. [43]</td>
<td>6760 men</td>
<td>45–64</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>8346 women</td>
<td></td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Meijer et al. [44]</td>
<td>3052 men</td>
<td>70</td>
<td>16.9</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>4663 women</td>
<td></td>
<td>20.5</td>
<td>1.2</td>
</tr>
</tbody>
</table>

IC, intermittent claudication.

Source: adapted from Cimminiello [45].
when the systolic blood pressures from both brachial arteries and that from both the dorsalis pedis and posterior tibial arteries are measured after the patient has been at rest in the supine position for 10 minutes using a continuous-wave Doppler device. It is computed as the ratio of each higher ankle to the higher of the two brachial systolic pressures. In healthy individuals, pulse wave reflection causes the ankle pressure to be 10–15 mmHg higher than the brachial arterial systolic pressure, and thus the normal ABI should be greater than 1.0. An ABI > 0.9 and < 1.4 is considered normal as these values are not associated with any detectable increase in cardiovascular ischemic risk (incident myocardial infarction [MI] or ischemic stroke). An ABI > 1.4 indicates non-compressible pedal vessels and an ABI ≤ 0.9 indicates hemodynamically significant arterial stenosis of the lower extremities [46]. The ABI will be addressed in more detail in Chapter 2, but we will briefly introduce the data showing validity of ABI in PAD diagnosis. The overall accuracy of the ABI to diagnose PAD has been well established. The comparative accuracy of an ABI threshold of 0.9 with angiography has been evaluated in various studies, notably by Fowkes et al. [47] and Lijmer et al. [48]. Fowkes et al. used an ABI threshold of 0.9 and showed that ABI has a sensitivity of 95% and a specificity of 100% compared with angiography to detect a ≥ 50% stenosis in peripheral arteries. Based on a receiver operating characteristic (ROC) analysis, Lijmer et al. demonstrated that an ABI threshold of 0.91 had a sensitivity of 79% and specificity of 96% to detect a 50% reduction in peripheral artery diameter. Multiple studies have also evaluated the inter- and intra-observer variability of the ABI measurement. One study evaluating inter-observer variability [49] found a standard deviation (SD) in differences in results of 0.07, suggesting that a reproducible change in ABI must be greater than 0.15 (2 SDs) to be significant. A second investigation [50] assessed 69 patients on six different days using the same technician, and found a measurement variance of 0.05. Based on these and other studies, the ABI is considered to have a reproducibility of approximately 0.10. The largest cohort to demonstrate this predominance of asymptomatic PAD was reported by Stoffers et al. [51] in a study performed in the Netherlands. The investigators evaluated 18 884 adults aged 45–74 years and showed a PAD prevalence of 6.9% based on an ABI < 0.95. However, only 22% of PAD patients had symptoms. The Rotterdam study [44] examined 7715 community-dwelling adults (40% men, 60% women) ≥ 55 years old. PAD diagnosis was determined using an ABI < 0.9 and claudication was diagnosed based on the WHO Rose questionnaire [52]. They found a PAD prevalence of 19.1% (16.9% in men and 20.5% in women), while claudication was present in only 1.6% (2.2% in men, 1.2% in women) of the population. Of the individuals with PAD, only 6.3% (8.7% in men, 4.9% in women) had claudication. The PAD Awareness, Risk and Treatment (PARTNERS) Study [13] focused on higher-risk individuals and evaluated 6979 primary care patients ≥ 70 years old, or 50–69 years old with a history of smoking or diabetes. As expected, the PAD prevalence was higher in this cohort (29%).
Older and frail individuals have a higher prevalence of PAD and are less likely to report symptoms due to their poor functional status. The Cardiovascular Health Study [53] found a 12% PAD prevalence among community-dwelling adults 65 years and older, and the Systolic Hypertension in the Elderly Program [42] reported a 25.5% prevalence. These two populations included healthier elderly adults. However, McDermott et al. [54], reporting results of an analysis among participants in the Women’s Health and Aging Study (an observational study of disabled women ≥ 65 years of age living in and around Baltimore), found a PAD prevalence of 35%, of whom 63% were asymptomatic. Also, PAD prevalence reported in a study of 60 nursing home residents was 88% [55].

Other studies have used additional markers to the ABI to define the PAD population. The Edinburgh Artery Study [12] assessed PAD based on claudication among a cohort of 1592 individuals aged 55–74 years using the WHO questionnaire. They also measured ABI and added an assessment of the change in ankle systolic pressure during reactive hyperemia. The prevalence of claudication in this cohort was 4.5%, while there were 8% of the population who were asymptomatic, yet had significant impairment of blood flow to the lower extremities (ABI < 0.7 or hyperemic systolic pressure drop of > 35%; or ABI < 0.9 and hyperemic systolic pressure drop of > 20%). Criqui et al. [10] conducted another study to evaluate PAD prevalence among 613 adults in southern California, with an average age of 66 years. They used a series of noninvasive vascular diagnostic tests (segmental blood pressure, Doppler-derived flow velocity, post-occlusive reactive hyperemia, and pulse-reappearance halftime). They found a prevalence of PAD of 11.7%. However, the prevalence of claudication in this population was 2.2% in men and 1.7% in women.

Claudication

Many epidemiological studies have used claudication as a marker for estimating the prevalence and incidence of PAD. Many patient questionnaires have been developed to identify intermittent claudication and to distinguish it from other types of leg pain. The first to be developed for use in epidemiologic studies in 1962 was the Rose questionnaire [44], which was eventually adopted by the WHO in 1968. The initial study evaluating the reliability of this questionnaire among 37 patients with classic claudication (angiographically confirmed PAD) and 18 patients with atypical leg pain (sciatica, osteoarthritis, and calf cramps), had a 91.9% sensitivity and 100% specificity. Not surprisingly (considering prior information in this chapter), larger studies performed more recently that used ABI as a comparison found a sensitivity of 8.6% [56] and sensitivity of 91% for diagnosis of PAD. Another leg symptom detection questionnaire, the Edinburgh claudication questionnaire (ECQ) [36], was developed in 1992. Further, the San Diego claudication questionnaire (SDCQ) [57] was developed
Prevalence and Incidence

in 1996. The SDCQ was a revised and expanded version of the WHO/Rose questionnaire and incorporated laterality.

Overall, the estimated prevalence of claudication assessed by an intermittent claudication questionnaire ranges from 0.4% in the 30- to 34-year-olds to at least 8% in the 70- to 74-year-olds [19] (Figure 1.4). Finnish investigators in the 1960s [58] interviewed 5738 men and 5224 women aged 30–59 years and found a prevalence of claudication of 2.1% in males and 1.8% in females. Scottish investigators [59] also found similar prevalence of claudication (1.8%), while Diehm et al. [60] in Germany documented claudication in 2.8% of adults aged 65 and older. Ness et al. [61] examined and interviewed 467 and 1444 elderly men and women (mean age 80 years) in an academic outpatient geriatrics practice. They found a 20% prevalence of claudication in the men and 13% in the women. Again, it should be noted that only a minority of patients with PAD would have classic claudication. To further illustrate this, we present the prevalence of claudication against the actual prevalence of PAD in various studies (Table 1.2).

Kannel and McGee [35] examined 26-year follow-up data of the Framingham Study Cohort of 5209 subjects. They reported that 176 men and 119 women developed occlusive peripheral arterial disease manifested as claudication. They also demonstrated that the incidence of claudication increased sharply with age until 75 years of age, with about a twofold male predominance at all ages. Their findings supported the evidence that elderly people (>60 years) suffer the most from claudication. Notably, at around 50 years of age, the prevalence of claudication is thought to be about 1–2%. At > 50 years, the estimated biannual incidence of claudication is 0.7% in males and 0.4% in females.
Atypical Leg Pain

Most individuals with lower extremity PAD do not have classic (typical) claudication but may have more subtle impairments of lower extremity function. Historically the WHO Rose questionnaire and other surveys of claudication have categorized PAD patients as symptomatic (claudication) or asymptomatic. However, many individuals with PAD have leg symptoms that are not claudication but cannot be completely attributed to other etiologies. For example, leg pain may persist or be present at rest in a patient without CLI, or the patient may have difficulty distinguishing pain syndromes from other etiologies, such as lumbar disc disease, from PAD. The San Diego claudication questionnaire allowed for lateralization of leg symptoms and added an atypical category to the original leg symptom characterization by the Rose questionnaire. Hirsch et al. [13], employed the questionnaire among 6979 high risk patients (≥70 years or 50–69 years with history of smoking or diabetes). Among people with a new diagnosis of PAD, only 6% had claudication, 48% were asymptomatic, 46% had atypical leg pain, and only 6% had typical claudication. Among those with prior diagnosis of PAD, only 13% had claudication; 26% were asymptomatic, and 62% had atypical leg pain. One report [54] evaluated upper and lower extremity functioning in 933 women enrolled in the Women’s Health and Aging Study. Among women with PAD (ABI < 0.9) in this cohort, 63% had no exertional pain. However, even these asymptomatic individuals had evidence of worse lower extremity physical function, defined by a slower walking velocity, poorer standing balance score, slower time to rise from a seated position, and fewer blocks walked per week. These findings go on to buttress the fact that individuals with atypical leg pain are at least as impaired as those with typical claudication. In our experience in clinic, we note that atypical leg pain is much more common than expected, with up to 70% of referred PAD patients having atypical symptoms or a mixture of typical and atypical features.

Critical Limb Ischemia

A chronic and severe decrease in leg perfusion may lead to CLI, defined by ischemic rest pain, non-healing wounds and gangrene. The term “CLI” has traditionally implied a high risk of amputation if leg perfusion is not improved. Yet, the true natural history of CLI is not well studied and has been indirectly (and probably inaccurately) estimated from rates of limb revascularization and ischemic amputation. In individuals over 50 years who have higher prevalence of claudication, CLI is thought to have a 1% prevalence. Among high-risk individuals the prevalence could be as high as 12%. In the highest risk group – those 70 years and older, or in those aged 50–69 years who smoke or have diabetes – the prevalence is estimated to approach 29% [13].
More objectively, in 2006, Jensen et al. [62] estimated CLI prevalence in Norway using a questionnaire among 20,291 men and women aged 40–69 years. CLI was defined as non-healing wounds or rest pain. They reported a CLI prevalence of 0.26% in men and 0.24% in women. More recently (2014), Nehler et al. [37] investigated a large US sample (about 12 million adults with health insurance) for PAD and CLI incidence and prevalence based on insurance claims between 2003 and 2008 and reported an annual CLI incidence of 0.35% and overall prevalence of 1.33%.

**Acute Limb Ischemia**

Acute limb ischemia is limb ischemia resulting from thrombotic, embolic, or traumatic arterial occlusion, with symptoms and signs developing over a period of two weeks or less [63]. Data for incidence of ALI are sparse. Using a survey of vascular surgeons in Great Britain and Ireland, Campbell et al. [64] reported 539 episodes of acute lower limb ischemia in a 3-month period. This translates to an estimated incidence of 3.7/100,000 people per year in the general UK population. Note that these data are for the lower extremity alone. The US estimate of ALI (both lower and upper extremity) was reported by Dormandy et al. in 1999 [65] as 14/100,000 people per year. It is important to note that ALI is a surgical emergency and that delayed treatment beyond 6 hours can lead to permanent disability. Amputation and mortality rates for ALI are 13% and 10%, respectively, and increase with delayed diagnosis and treatment [66, 67].

**Risk Factors for Development of PAD**

Systemic atherosclerosis is the main cause of PAD. Although it is difficult to determine the exact time of PAD incidence in a particular individual, given that it is often asymptomatic ( unlike stroke, for example), the same risk factors have demonstrated an association with incident PAD in multiple studies. Further, it is also biologically plausible to assert that the same risk factors that contribute to the development and propagation of atherosclerosis in other vascular beds also lead to the initiation and worsening of PAD, although some (especially tobacco use and diabetes) are known to be most strongly associated with PAD incidence. Major PAD risk factors include age (which has been extensively covered), cigarette smoking, diabetes, hypertension, and hyperlipidemia. Others include elevated C-reactive protein (CRP) levels and hyperhomocysteinemia. Figure 1.5 [68] displays the ORs of major PAD risk factors in HICs and LMICs that were defined in a recent global report which performed a meta-analysis of the effect size of 14 risk factors that were investigated in at least three retained studies using multivariate design. We will now focus on each of the major risk factors of PAD.
As early as the 1970s, smoking has been recognized as an incredibly powerful risk factor for PAD [69]. Cigarette smoke causes endothelial dysfunction by reducing nitric oxide-dependent vasodilation, leading to increased atherosclerosis [70]. Analysis of the Edinburgh Artery Study [71, 72] showed that smokers are up to three times more likely to have PAD than coronary artery disease. The odds ratio for smoking in PAD ranged from 1.8 to 5.6, while that for smoking and heart disease ranged from 1.1 to 1.6. In the Framingham study [73], about 80% of individuals with claudication smoked. Smoking increases the risk of PAD by up to sevenfold [25, 51] and there also appears to be a dose–response relationship between smoking (including number of cigarettes smoked per day and number of years smoked) and PAD [72]. Secondhand smoke exposure has also been shown to lead to a 1.67-fold increased risk of developing PAD [74].

In the recent global report by Fowkes et al. [23], smokers had a 2.72-fold higher odds for developing PAD than non-smokers in HICs and 1.42-fold in LMICs. Ingolfsson et al. [33], using Poisson regression, showed in Iceland that rates of claudication dropped from 1.7/1000 per year in 1970 to 0.6/1000 per year in 1984 in younger men and from 6.0 to 2.0 in those aged 70 years and older. This drop was attributed to decreased smoking and cholesterol levels. Other studies have shown that smoking cessation leads to a reduction in
Risk Factors for Development of PAD

Claudication symptoms and mortality [75, 76]. Smoking also reduces the chances of success of surgical revascularization procedures in PAD patients and increases risk of amputation [33].

**Diabetes Mellitus**

The risk of claudication in diabetics has been found to be at least double that in nondiabetics [77]. Further, CLI and amputation occur up to 10 times more frequently among diabetic PAD patients than among their counterparts without diabetes [78]. In individuals without diabetes who have insulin resistance, the risk of PAD is higher than in those who do not have insulin resistance [79]. Risk is also higher among non-diabetics with hyperinsulinemia [80].

Diabetes has been shown by multiple studies to be associated with a two- to fourfold increased risk of PAD [24, 51, 53]. Hiatt et al. [21] showed that up to 20% of PAD patients are also diabetic; furthermore, the attributable fraction of diabetes for incident PAD was about 14% [81]. In the Framingham Heart Study [35], diabetes had an OR of 3.5 in men and 8.6 in women for risk of PAD. The longer a person has diabetes, the more likely it is that he or she will develop PAD. In one study [82], newly diagnosed diabetes had only borderline association with incident PAD. Globally, the OR of PAD in diabetics is 1.88 in HICs and 1.47 in LMICs compared with non-diabetics. Diabetics with PAD have worse outcomes and increased progression to CLI than do non-diabetics with PAD. Diabetics are up to 15 times more likely to develop CLI and undergo an amputation [83] and have a threefold higher mortality than non-diabetics with PAD [84].

**Dyslipidemia**

Historically, there have been conflicting reports concerning the effect of dyslipidemia on PAD risk. The Edinburgh Artery Study found an increased risk of PAD with elevated total cholesterol and a reduced risk with elevated high-density lipids (HDLs) [72]. Meijer et al. [44] and Newman et al. [53] also found a positive association between total cholesterol and PAD. In the analysis of the Framingham study by Kannel et al. [30] PAD risk was two times higher with cholesterol levels > 270 mg/100 mL. However, when Murabito et al. [25] analyzed the Framingham data using a total cholesterol threshold of 240 mg/100 mL, this relationship was attenuated. In a multivariate analysis among elderly individuals, Ness et al. [61] did not find a significant association between total cholesterol and PAD; neither did Hughson et al. [69], Zimmerman et al. [85], or Criqui et al. [79]. It is not surprising that total cholesterol is a risk factor with variable results given that low-density lipoprotein is a more significant pathological component of cholesterol. Overall, there are more studies showing a link between total cholesterol and PAD than there are that do not. Hypercholesterolemia has a population attributable
fraction for PAD of 17% [81]. More recently, the global estimates for PAD risk related to hypercholesterolemia were 1.19 in HICs and 1.14 in LMICs [23].

Multiple studies, including those by Ness et al. [61] and Curb et al. [86], have confirmed the protective effect of HDLs on PAD risk. Although there is also some discrepancy in reports evaluating the link between hypertriglyceridemia and PAD, the majority [24, 25, 72] show a positive association. The Edinburgh Heart Study [72] showed only a univariate association with triglycerides.

**Hypertension**

Hypertension is associated with an increased risk of PAD. Studies that dichotomized hypertension as yes/no demonstrated an increase in risk of PAD ranging from 1.32-fold, as observed in the Rotterdam study [51], to 2.2- (men) and 2.8-fold (women), as observed by Ness et al. [61]. In the Framingham cohort, Kannel et al. [35] found an OR of 2.5 in men and 4.0 in women for the association of hypertension and PAD. However, in Finland, Reunanen et al. [15] interviewed 5738 men and 5224 women aged 30–59 years and did not find a significant association between hypertension and claudication. The most recent global report that examined PAD risk factors [23] reported that hypertension had a 1.55 (in HICs) and 1.36 (in LMICs) increased risk of PAD.

Some reports have examined systolic and diastolic blood pressure. In the report by Fowkes et al. [72], for each 10 mmHg rise in systolic blood pressure, there were ORs of 1.2 (univariate model) and 1.1 (multivariate model) (both significant) for claudication. There was no association between diastolic blood pressure and PAD. Other studies have corroborated the link between systolic blood pressure and PAD, and diastolic pressure does not have a significant association [51, 53]. Due to the high prevalence of hypertension, the population risk of PAD attributable to hypertension is reported as 41% [81].

**Homocysteinemia**

Since the 1980s [87, 88], homocysteinemia has been shown to be associated with an increased risk of PAD. In 1998, Aronow et al. [89] examined 147 men and women with PAD and 373 men and women without PAD with a mean age of 81 years. They found that plasma homocysteine was a significant independent risk factor for PAD with an OR of 1.13 for each 1 µmol/L increase. One meta-analysis in 1995 showed an OR of 6.8 (95% CI: 2.9–15.8) for a 5 µmol/L difference in fasting total homocysteine [90]. The OR found in this study for CAD was 1.6 for men and 1.8 for women. Another meta-analysis of 14 studies in 2009 [91] showed that homocysteine was significantly elevated, with a pooled mean difference of +4.31 µmol/L in PAD patients compared with controls. Robinson et al. [92] reported that homocysteine concentrations > 12.1 µmol/L are associated with a twofold increased risk of atherosclerotic vascular disease (PAD, CAD and stroke). It has been reported that up to 40% of PAD patients
have elevated homocysteine levels and that the levels are even higher in those with claudication [93, 94]. Increased homocysteine levels also increase the risk of PAD progression [93]. Recently, Khandanpour et al. [91] evaluated the effect of folate supplementation on PAD among eight clinical trials, but there was inconsistency in the reported outcomes. However, there are no randomized studies indicating that treating homocysteine reduces progression of disease.

C-Reactive Protein and Fibrinogen

Serologic markers of inflammation associated with systemic atherosclerosis are also associated with PAD. Among healthy volunteers enrolled in the Physicians’ Health Study [95], both CRP and fibrinogen were found to be significantly associated with PAD. Multivariate analyses showed ORs of 2.8 for CRP and 2.2 for fibrinogen in the upper quartile compared with the lowest quartile. In this study, CRP was highest in those who ultimately required vascular surgery. In a case–control study with 212 cases and 475 controls, all female aged ~ 50 years, Bloemenkamp et al. [96] found that elevated CRP levels were associated with PAD (OR = 3.1 for women in the fourth quartile compared with women in the first quartile). Among elderly individuals in the Honolulu Heart Program [86], fibrinogen had an OR of 1.28 for PAD risk.

In multivariable models adjusting for traditional cerebrovascular disease (CVD) risk factors in the MESA study [97], CRP was not significantly associated with PAD. However, other markers of inflammation, including interleukin-6 (IL-6), fibrinogen, D-dimer, and homocysteine, showed significant associations with PAD, with the highest OR being 1.29 (1.08–1.53) for IL-6.

Obesity

Although obesity is associated with an increased risk of atherosclerotic diseases, including stroke and CAD [98], it does not appear to be positively associated with PAD. In fact, most studies have shown a negative association with higher BMI related to lower PAD risk. In a cross-sectional analysis of the MESA study [97], a 1 kg/m² increase in body mass index (BMI) was associated with a slightly lower prevalence of PAD (OR = 0.97, 95% CI: 0.94–0.99). This was similar to findings by Newman et al. [53] in CHS that BMI reduced risk of PAD (OR = 0.94, 95% CI: 0.91–0.97). In the cross-sectional analysis of the Honolulu heart study [86], a 1 kg/m² increase in BMI also showed 36% reduced odds of PAD. However, BMI was not significantly associated with PAD in the longitudinal analysis of the same study (OR = 0.92, 95% CI: 0.76–1.11). More recently, in Fowkes et al.’s global meta-analysis [23], BMI used as a continuous variable (per 1 kg/m² increase) did not show any association with PAD. However, BMI when dichotomized (> or ≤ 25 kg/m²) showed a reduced risk of PAD in LMICs (OR = 0.72, 95% CI: 0.63–0.81) but there was no association with PAD in HICs (OR = 0.96, 95% CI: 0.84–1.10). The overall global association was however
significant (OR = 0.83, 95% CI: 0.75–0.91). In the Framingham Study [35], claudication was significantly inversely related to relative weight in men in multivariable analysis and seemed to have a U-shaped non-linear relationship with relative weight in women. One study that showed increased risk of PAD with higher BMI was conducted among over 10 000 middle-aged men in Israel [34], and reported an OR of 1.24 for incident claudication for each 5.0 kg/m² increase in BMI.

One possible explanation for these findings is that BMI may not be the best indicator for obesity in individuals aged 60 years and above [99]. Douketis and Sharma [100] suggested that in older people, because of loss of lean body mass, BMI can remain unchanged or even decrease although adiposity increases. One study that lends more credence to this is that conducted by Ix et al. [101]. In that study, the authors hypothesized that the previous findings in the BMI/PAD association may be due to lower weight among smokers and those with poor health status. In the general population of 5419 adults ≥ 65 years old, each 5-unit increase in BMI was inversely associated with PAD (prevalence ratio [PR] = 0.92, 95% CI: 0.85–1.0). However, among persons in good health who had never smoked, the direction of the association was opposite but not statistically significant (PR = 1.2, 95% CI: 0.94–1.52). When results were calculated among never smokers in good health, using BMI at 50 years old and prevalent PAD, or at baseline and incident PAD, a positive association was found – PR = 1.30, 95% CI: 1.11–1.51, and hazard ratio = 1.32, 95% CI: 1.0–1.76, respectively.

Some studies have shown that higher waist:hip ratio rather than BMI or body fat percentage is associated with higher risk of PAD [102–104], suggesting that central adiposity may be more closely related to an increased risk of PAD. More research is needed to define the true relation between obesity and PAD, but it would appear that the relationship is more likely to be U-shaped.

Other Risk Factors

Multiple non-traditional risk factors for PAD have been studied. Hypothyroidism has been shown to be associated with increased PAD risk, especially in older individuals. One study [105] in 249 men and women with a mean age of 79 years showed a significantly higher prevalence of PAD in individuals with subclinical hypothyroidism (78%) than in those who were euthyroid (17%).

Few PAD studies, including the MESA and ARIC studies, are multi-racial. These permit comparisons of the effect of race on PAD. Allison et al. [97] reported results from the MESA study showing an OR of PAD of 1.67 for blacks vs non-Hispanic whites. ARIC also showed a higher prevalence of PAD in blacks compared with whites (3.3% vs. 2.3% in males and 4.0% vs. 3.3% in females) [43]. Among Asians, the results from the Honolulu Heart Program suggests a lower PAD prevalence than comparable non-Hispanic whites [86].
The Strong Heart Study [106] showed prevalence estimates among Native Americans, similar to that reported in comparable non-Hispanic whites. Results from MESA [97] and the San Diego Population Study [107] suggest that PAD rates may be lower in Asians and Hispanics than in non-Hispanic whites. Hence PAD risk is highest in blacks, followed by Native Americans, non-Hispanic whites, Hispanics and Asians.

Various studies have shown conflicting results with alcohol intake and PAD. The Edinburgh Artery Study [108] showed a protective effect of alcohol in men but not in women. Although the association became non-significant after adjustment for socioeconomic class. In elderly Japanese American men in the Honolulu Heart study [86], alcohol intake was found to increase the risk of PAD (multivariate OR = 1.15, 95% CI: 1.02–1.31). Alcohol, however, had a protective effect among Native Americans in the Strong Heart Study [106]. Results from the Physicians Health Study [109] showed a protective effect of moderate alcohol intake in multivariate analysis. Interestingly, in that study, there was no association in the univariate analysis until after adjusting for smoking. This suggests that moderate alcohol use in otherwise healthy non-smokers may have a protective effect on PAD incidence.

Chronic kidney disease is associated with an increased risk of PAD [110, 111], as well as worse outcomes with PAD, including limb loss and mortality [112]. Regular physical activity has also been shown to have a protective effect on PAD with an OR of 0.51 [113]. Bowlin et al. [34] found that work problems, psychosocial coping mechanisms both at home and at work, anxiety (high vs. low; OR = 1.85, 95% CI: 1.29–2.65) and socioeconomic status were found to be associated with PAD. Of these, anxiety had the highest OR (1.85) for 5-year incident claudication. For people who already had PAD, McDermott et al. [114] showed that depressive symptoms led to worse outcomes. Poor oral health is also associated with PAD. When Navas-Acien et al. [115] examined over 2000 adults in the 1999–2000 National Health and Nutrition Examination Survey (NHANES), they found that elevated serum levels of lead and cadmium were associated with an increased prevalence of PAD. Hung et al. [116] showed that incident tooth loss was significantly associated with elevated risk of subsequent occurrence of PAD. In this study, among men with a history of periodontal diseases, tooth loss had a relative risk of 1.88 for PAD. There are also data suggesting that the presence of antiphospholipid antibodies in patients undergoing lower extremity bypass operations was a significant independent risk factor for progression of PAD [117]. Eraso et al. [118] found that lower circulating fetuin-A was associated with PAD in type 2 diabetes beyond traditional and novel cardiovascular risk factors. In a multivariable analysis, a 1 SD decrease in fetuin-A increased the odds of PAD (OR = 1.6, P = 0.02). Although there is evidence [119] that some of the variability in ABI could be explained by additive genetic effects, data for the genetic association of PAD have been inconsistent. However, a family history of PAD has been shown
to be associated with incident PAD in multivariate analyses both in the Framingham and San Diego Population Study cohorts [120, 121].

Recently, Duval et al. [122] derived a risk score to detect prevalent PAD in any given population. They used data from the REACH registry and externally validated it using the Framingham Offspring Study. PAD presence was determined by a history of previous or current claudication, lower extremity arterial intervention, or ABI < 0.9. Multivariable stepwise logistic regression was used to identify cross-sectional correlates of PAD from demographic, clinical, and laboratory variables. Age, sex, smoking, diabetes, BMI, hypertension, history of heart failure, CAD, and CVD were predictive of PAD prevalence. The model-estimated PAD prevalence corresponded closely with actual PAD prevalence in each population. The C-statistic was 0.61 for derivation, 0.60 for internal validation and 0.63 for external validation when ABI < 0.9 was used, and 0.64 when clinical PAD was used. This score can be used as a tool to validate a given estimate of PAD in a population.

**Awareness of PAD in the Community**

Despite the high prevalence and poor cardiovascular outcomes of PAD, the general public awareness of PAD risk remains low. The National Heart, Lung, and Blood Institute partnered with the national Peripheral Artery Disease Coalition and initiated a national PAD awareness campaign – Stay in Circulation: Take Steps to Learn About PAD – in 2003. The national Peripheral Arterial Disease Coalition, coordinated by the Vascular Disease Foundation, is an alliance of > 50 cardiovascular and vascular health professional societies, health advocacy groups, and government agencies united to provide accurate health information to those with or at risk for PAD. As part of this initiative, a survey of US adults was conducted in 2006 to determine the general public awareness of PAD [123]. The survey found that 74.2% of US adults were not aware of the meaning and risk factors of PAD. What is particularly striking is that the awareness of other diseases which are much less common than PAD exceeds that of PAD. Even among those who are aware of PAD, the awareness of the consequences remains low (Figure 1.6).

**Progression, Natural History, and Outcomes of PAD**

**Progression**

A few studies have evaluated PAD progression in various populations [31, 124–129]. The lowest estimate of progression in these studies is 2.5%/year developing rest pain or gangrene [125]. In this study, PAD progressed at a rate
of around three times greater in the first year after diagnosis than in subsequent years. Using ABI and posterior tibial peak forward flow velocity, Bird et al. [129] found a categorical progression of 3.7%/year (16.9% over 4.6 years of follow-up). The highest reported estimate of progression is 9.1%/year [127], and this was determined based on angiographic evidence of disease progression. Given that angiography will be most accurate, we propose that one would expect a 9–10% annual progression of PAD. Two of these studies estimated the average annual change in ABI. Fowkes et al. [128] calculated a change of
0.01/year, while the estimate from Bird et al. [129] was –0.02 over a 4.6-year follow-up.

Factors that increase risk of PAD also lead to progression of already established disease. In various studies, age [31, 129], smoking and diabetes [31, 129, 130], dyslipidemia [31, 129, 130], typical claudication, PAD in the contralateral leg and previous intervention [31], lipoprotein(a) and high-sensitivity CRP [130] have been shown to be independently associated with PAD progression in various patient groups. Diabetes seems to be a stronger factor in progression of PAD in smaller lower extremity arteries [130], while hypertriglyceridemia has been shown to be particularly important in predicting progression and onset of CLI among smokers [131]. Patients who develop PAD prior to the age of 45 (premature PAD) are more likely to have faster disease progression and worse outcomes, including limb loss and mortality [132, 133]. PAD may progress, especially in the infrapopliteal arteries, without significant change in the ABI [134].

Natural History and Outcomes

The systemic nature of the atherosclerotic process also contributes to development of concomitant disease of the arteries to the heart and brain. Consequently, patients with PAD have an associated increased risk of cardiovascular ischemic events, such as MI, ischemic stroke, and death [135]. The co-prevalence of PAD with other atherosclerotic diseases has been shown in multiple studies and highlighted all through this chapter. In fact, there is an inverse correlation between ABI and odds of a major cardiovascular event. There is an abundance of evidence to show that individuals who have PAD also suffer adverse cardiovascular outcomes, including myocardial infarctions, hospitalization and stroke, at rates that are at least similar to, and often higher than, those for individuals with established coronary artery disease [136–138]. Newman et al. [53], in their analysis of CHS, showed that rates of MI, congestive heart failure and stroke were up to two to three times as high among individuals with PAD compared with those without. Similarly, individuals with MI, congestive heart failure and stroke had a prevalence of PAD that was 2–2.5 times the prevalence in individuals without these conditions. Figure 1.7, adapted from an analysis of the placebo arm of the Appropriate Blood Pressure Control in Diabetes study [139], depicts this. Figure 1.8 shows the co-prevalence of atherosclerotic diseases.

When compared with healthy individuals, over 15 years of follow-up, survival rates of patients with advanced PAD (CLI) are worse than those seen in patients with PAD, which in turn are worse than those for healthy individuals [19] (Figure 1.9). The frequency of systemic cardiovascular adverse events is higher than that of limb events in PAD patients [1]. This has led to PAD being recognized as a coronary heart disease risk equivalent (i.e., with PAD, there is
Figure 1.7  Adjusted odds of a cardiovascular event by ankle–brachial index (ABI). Data from the placebo arm of the Appropriate Blood Pressure Control in Diabetes study. CV, cardiovascular; MI, myocardial infarction. Source: adapted with permission from Mehler et al. [139].

Figure 1.8  Typical overlap in vascular disease affecting different territories. Based on Reduction of Atherothrombosis for Continued Health (REACH) registry data. PAD, peripheral artery disease. Source: adapted with permission from Norgren et al. [19].

a > 20% risk of a coronary event in 10 years) in international treatment guidelines in the US and Europe [1, 140]. Figure 1.10, adapted from the ACC/AHA 2005 practice guidelines for the management of patients with peripheral
arterial disease (lower extremity, renal, mesenteric, and abdominal aortic) [1], summarizes the natural history of PAD.

**Summary**

Peripheral artery disease encompasses disorders of the structure and function of all non-coronary arteries, and specifically refers to atherosclerotic disease of lower extremity arteries. Five clinical syndromes characterize PAD. These are asymptomatic PAD, claudication, atypical leg pain, ALI and CLI.

Peripheral artery disease affects most adult populations worldwide irrespective of socioeconomic or national developmental status. The prevalence of PAD depends on what clinical syndrome defines it in a particular epidemiological study. The prevalence of claudication is lower than the prevalence of asymptomatic PAD measured by ABI. With increasing age (45–89 years), global prevalence of PAD among women ranges from 2.7% to 24.2% in HICs, and 3.96% to 18.65% in LMICs. Among men, global prevalence ranges from 2.76% to 24.77% in HICs, and 1.21% to 21.5% in LMICs.

Tobacco use, diabetes mellitus, increasing age, hypertension and hyperlipidemia are major risk factors for development and progression of PAD. Other risk factors have been described, including elevated CRP, hyperhomocysteinemia, chronic kidney disease, hypothyroidism, obesity, lower circulating fetuin-A, and periodontal disease. The systemic nature of the atherosclerotic process also contributes to development of concomitant disease of the arteries to the heart and brain. Consequently, patients with PAD have an associated increased risk of cardiovascular ischemic events (MI, stroke, and death).
Natural history of atherosclerotic lower extremity PAD syndromes

PAD population (≥ 50 years)

Initial clinical presentation

- Asymptomatic PAD: 20–50%
- Progressive functional impairment
- Atypical leg pain: 40–50%
- Claudication: 10–35%
- Critical limb ischemia: 1–2%

1 year outcomes

- Alive with two limbs: 50%
- Amputation: 25%
- CV mortality: 25%

CV causes: 75%

Non-CV causes: 25%

5 year outcomes

- Limb morbidity
  - Stable claudication: 70–80%
  - Worsening claudication: 10–20%
  - Critical limb ischemia: 1–2%
  - Amputation (see CLI data)

- CV morbidity and mortality
  - Non-fatal cardiovascular event (MI or stroke): 20%
  - Mortality: 15–30%
  - CV causes: 75%
  - Non-CV causes: 25%

Figure 1.10 The natural history of peripheral artery disease (PAD). CV, cerebrovascular; MI, myocardial infarction; CLI, critical limb ischemia. Source: adapted with permission from Norgren et al. [19].
Despite the high prevalence and poor cardiovascular outcomes of PAD, the general public awareness of PAD risk remains low, and over 70% of US adults are not aware of the meaning and risk factors of PAD. More work needs to be done to improve awareness of PAD in the community.

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