Chapter 2
Role of the Ankle Brachial Index

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Lower extremity peripheral artery disease (PAD) affects 8.5 million men and women in the United States and more than 200 million people worldwide [1, 2]. People with PAD have a two- to threefold increased rate of cardiovascular events and all-cause mortality compared to people without PAD [3, 4]. People with PAD also have greater functional impairment and faster functional decline than people without PAD [5–10]. Medical management of PAD consists of preventing cardiovascular events, improving functional performance, and stopping functional decline. To prevent cardiovascular events, people with PAD should undergo treatment with preventive medications, including cholesterol-lowering drugs such as statins and antiplatelet therapy [11]. To improve walking performance, people with PAD should be helped to engage in regular walking exercise activity [11–13]. Diagnosing PAD is important so that appropriate therapies can be implemented to prevent cardiovascular events, improve walking performance, and prevent mobility loss. The ankle brachial index (ABI) is a reliable, sensitive, and highly specific noninvasive test for PAD and can be used to diagnose and assess the severity of PAD. This chapter provides an overview of the role of the ABI in diagnosing PAD and in assessing risk of cardiovascular outcomes, lower extremity outcomes, and functional decline.

Symptoms of Peripheral Artery Disease

Intermittent claudication has been considered the most classical symptom of PAD [14, 15]. Symptoms of intermittent claudication consist of exertional calf pain that does not begin at rest and that resolves within 10 min of rest. Intermittent

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C. M. Kramer (ed.), *Imaging in Peripheral Arterial Disease*,
https://doi.org/10.1007/978-3-030-24596-2_2

claudication symptoms due to PAD were originally described by Dr. Geoffrey Rose, a London epidemiologist, who developed the Rose intermittent claudication questionnaire in the 1960s, based on observations of patients with PAD. The questionnaire was developed for use in epidemiologic studies, facilitating a standardized approach to measuring the incidence, prevalence, and significance of PAD in epidemiologic studies. Using the Rose claudication questionnaire to diagnose PAD, the prevalence of claudication is approximately 1–3% among community dwelling men and women over age 50 [16, 17].

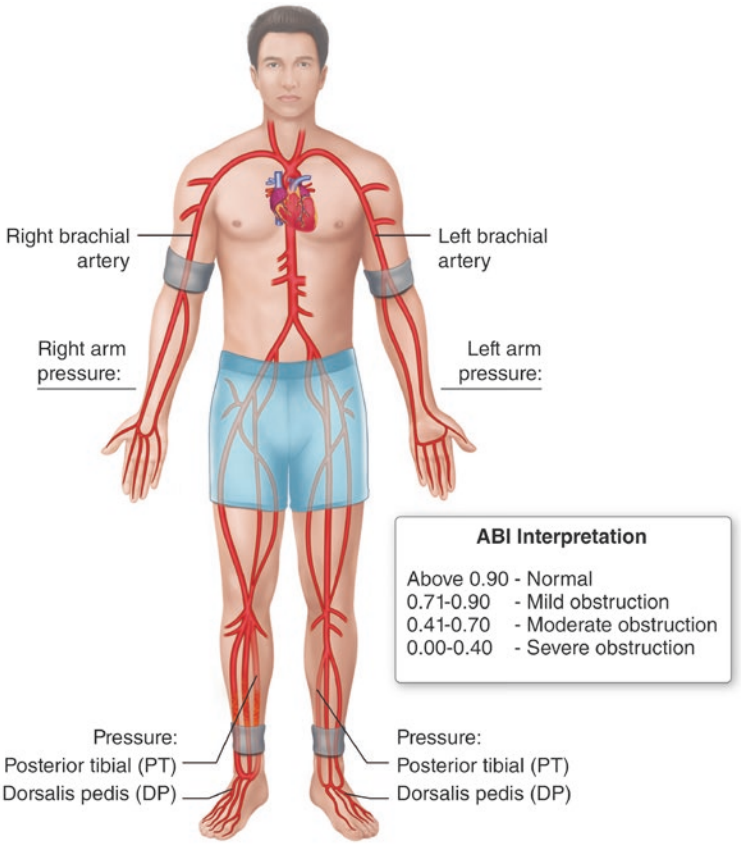
However, it is now well recognized that most people with PAD do not have classical symptoms of intermittent claudication [15–18]. Many people with PAD are asymptomatic (i.e., have no exertional leg symptoms), and others have exertional leg symptoms that are atypical for classical intermittent claudication symptoms (i.e., atypical exertional leg symptoms) [15–18]. Among people with PAD, the prevalence of asymptomatic PAD varies from 20% among those identified from a noninvasive vascular laboratory to approximately 67% among community dwelling older men and women [16–18]. Asymptomatic PAD is due in part to physical activity restriction in people with PAD. Specifically, people with PAD restrict their physical activity in order to avoid leg symptoms and become so sedentary that they report no exertional leg symptoms [5, 15]. Other people with PAD slow their walking speed to avoid ischemia leg symptoms with walking [5, 9, 10, 18]. Many people with PAD who report no exertional leg symptoms also have undiagnosed, unrecognized PAD [15].

The prevalence of atypical ischemic leg symptoms, defined as exertional leg symptoms that do not meet criteria for classical intermittent claudication, is approximately 30 to 50% in people with PAD [15]. Atypical exertional leg symptoms in PAD may be related in part to the high prevalence of comorbidities affecting the lower extremities in people with PAD, including peripheral neuropathy, spinal stenosis, and degenerative arthritis of the hips, knees, and spine [10, 15, 16]. These comorbidities can also cause leg symptoms on exertion. Distinguishing leg symptoms due to comorbidities from leg symptoms due to peripheral artery disease can be difficult.

The ABI is a sensitive and highly specific noninvasive diagnostic test that detects PAD even in the absence of symptoms and in the presence of atypical exertional leg symptoms. The role of the ABI as a diagnostic tool is underscored by the fact that most people with PAD do not have classical symptoms of intermittent claudication. Increased rates of cardiovascular events, functional impairment, and functional decline are observed even in people with asymptomatic PAD and in people with PAD accompanied by atypical exertional leg symptoms [3–15]. The ABI can be a useful tool for diagnosing people with PAD who are at increased risk of cardiovascular events, mortality, and functional decline. Furthermore, the ABI value provides prognostic information regarding magnitude of risk for each of these outcomes.

Overview of the Ankle Brachial Index

The ABI is a ratio of Doppler-recorded systolic pressures in the lower and upper extremities (Fig. 2.1). In healthy people without PAD, arterial pressures increase



Right ABI						Left ABI
Lower right ankle pressure / Higher arm pressure	=	mm Hg / mm Hg	= — —	Lower Left ankle pressure / Higher arm pressure	=	mm Hg / mm Hg = — —
Example	Lower right ankle pressure / Higher brachial pressure	=	92 mm Hg / 164 mm Hg	= 0.56	See ABI chart	

Fig. 2.1 The ankle brachial index measurement

with greater distance from the heart. This occurs because of retrograde wave reflection generated by resistance from peripheral arterioles that adds to retrograde flow [19]. Additionally, increasing impedance with increasing arterial taper contributes to increasing systolic pressures with increasing distance from the heart [19]. This phenomenon results in higher systolic pressures at the ankle compared to the brachial arteries in people without lower extremity arterial obstruction. For these reasons, people without lower extremity atherosclerosis typically have an ABI value $\geq$1.10 and <1.30. As described below, an ABI value >1.30 is indicative of medial calcinosis of lower extremity peripheral arteries and may be commonly observed in people with and without PAD.

The ABI as a measure of the presence and severity of PAD has been validated against angiographically documented PAD. Using an angiogram-demonstrated stenosis of 50% or greater to diagnose PAD, Lijmer et al. reported that an ABI <0.91 had a sensitivity of 79% and a specificity of 96% for PAD in approximately 100 limbs [20]. An ABI of 1.19 had sensitivity of 94% and specificity of 29% for PAD [20]. In a population of 298 consecutive patients from China (199 men) who underwent lower extremity digital subtraction angiography (DSA) and the ABI, more severe PAD measured by DSA was associated with lower ABI values [21]. Using DSA-measured luminal stenosis of 0.50 or greater as the threshold for PAD, an ABI value <0.95 maximized sensitivity (91% sensitive) and specificity (86% specific) for diagnosing PAD, compared to alternative ABI thresholds. Ouriel et al. reported that an ABI <0.97 was 94% sensitive and 99% specific for PAD [22]. In summary, the ABI is both sensitive and specific for PAD, with lower ABI values indicative of more severe lower extremity atherosclerosis.

Ankle Brachial Index Measurement

The ABI should be measured with the patient in a supine position, after at least a 5 min rest (Box 2.1). Appropriately sized blood pressure cuffs are placed over each brachial artery and at each ankle. At the ankle, the blood pressure cuff bladder should be positioned so that the artery marker is directly over the posterior tibial artery. Patients should be instructed not to talk during the examination, since talking

Box 2.1 Measuring the Ankle Brachial Index

- The ankle brachial index (ABI) should be measured in the supine position.
- The patient should rest supine for at least 5 min before the measurement is performed.
- A 5–10 mHz Doppler and appropriately sized blood pressure cuffs for each extremity are required.
- Pressures are measured beginning with the right brachial artery followed by the right dorsalis pedis, right posterior tibial, left dorsalis pedis, left posterior tibial, and left brachial arteries.
- The Doppler probe should be used to locate the strongest signal from each artery.
- The sphygmomanometer is inflated to at least 20 mm above the systolic pressure.
- The sphygmomanometer should be deflated no faster than 2 mm/s.
- The ABI may be calculated for each artery but is typically calculated for each leg by dividing the highest lower extremity pressure in each leg by the highest brachial artery pressure.

can alter the systolic pressures during the test. Blood pressures are typically measured sequentially starting with the right upper extremity to the right lower extremity, left lower extremity, and left upper extremity. In the lower extremities, the dorsalis pedis and the posterior tibial pressure are each measured. However, if time is insufficient for measuring both the dorsalis pedis and posterior tibial arteries in each extremity, accurate ABI values can also be obtained by measuring the posterior tibial artery alone [20]. A handheld Doppler is used to locate each artery before each arterial pressure measurement. The probe should be moved so that it detects the strongest signal from the artery prior to cuff inflation. Accurate ABI measurement consists of inflating the cuff sphygmomanometer to at least 20 mm above the systolic pressure and deflating the pressure no faster than 2 mm/s. The systolic pressure at which the pulse reappears is measured and recorded for each artery and used to calculate the ABI as described below.

Calculating the ABI

The ABI is the ratio of Doppler-recorded systolic pressures in the lower and upper extremities. An ABI may be calculated for each lower extremity artery, by dividing the lower extremity artery pressure by the highest of the brachial artery pressures. The ABI is typically calculated for each leg, by dividing the highest of the two pressures in each leg by the highest of the left vs. the right brachial artery pressures. The highest pressure in each leg is traditionally selected when calculating the ABI, because the highest pressure represents the greatest arterial pressure reaching the foot. However, it has been demonstrated that the ABI calculation using the average of the dorsalis pedis and posterior tibial artery pressures correlates most closely with functional impairment in people with PAD [23]. Using the lowest of the dorsalis pedis and posterior tibial pressures to calculate the ABI in each leg maximizes sensitivity of the ABI for the diagnosis of PAD [24] but may be associated with lower specificity.

Interpreting ABI Values

A normal ABI value is defined as an ABI between 1.10 and 1.30 (Table 2.1). An ABI value of <0.90 is 99% specific and approximately 79% sensitive for the presence of PAD [20]. ABI values <1.00 are more sensitive for PAD than ABI values of <0.90 [22]. For example, as noted above, an ABI <0.97 was reported to be 94% sensitive for PAD [22]. Among people with ABI <0.90, lower ABI values indicate more severe PAD [21]. ABI values <0.50 are associated with increased risk of amputation compared to higher ABI values in patients with leg ulcers and in patients with history of diabetes values [25, 26].

Table 2.1 Ankle brachial index values and their clinical significance

ABI value	Clinical relevance	Associations with clinically important outcomes
1.10–1.30 (reference)	Absence of lower extremity atherosclerosis	Associated with lower rates of cardiovascular events and better lower extremity functioning than ABI values <1.1.0
0.90–1.10	Small amounts of lower extremity atherosclerosis	People with ABI 0.90–1.10 have slightly higher rates of all-cause mortality, cardiovascular events, and mobility loss compared to the reference group
0.50–0.90	Indicates the presence of mild to moderate PAD	Risk of all-cause mortality, cardiovascular events, and mobility loss is significantly higher than the reference group
<0.50	Indicates severe PAD	Risk of all-cause mortality, cardiovascular events, and mobility loss is significantly higher than the reference. Increased risk of lower extremity limb loss or critical limb ischemia
> 1.30	Indicates lower extremity medial calcinosis and inability to assess the presence and severity of lower extremity atherosclerosis	Increased risk of mortality and cardiovascular events compared to the reference

Interpreting the ABI Value in People with Diabetes Mellitus and Those with Medial Calcinosis of Lower Extremity Arteries

An ABI <0.90 may be less sensitive for PAD in people with diabetes, due to medial calcinosis, a phenomenon in which calcification of the media in the lower extremity arterial wall results in arterial stiffness and an increased arterial pressure at the ankle. This phenomenon of increased lower extremity arterial pressures results in an artificially higher ABI value and lower sensitivity for PAD. Although data are variable, an ABI <0.90 is typically less sensitive for PAD in people with diabetes, compared to those without diabetes [27, 28]. Medial artery calcinosis is also observed in older people and in people with end-stage renal disease. People with incompressible lower extremity arteries who have systolic pressures >300 mm Hg at the ankle have ABI values >1.30. In these individuals, the ABI is not a reliable measure of lower extremity arterial obstruction, and alternative methods (such as toe pressures or Doppler waveform analyses) must be used to diagnose PAD. The toe pressure is useful for patients with non-compressible lower extremity arteries, because the digital vessels typically do not develop calcifications and therefore can be accurate measures of lower extremity arterial disease. In people suspected of having PAD who have a normal ABI, noninvasive lower extremity arterial duplex testing and toe pressure testing are the best methods to diagnose PAD, since neither measure is affected by medial calcinosis of the lower extremity arteries [19]. Although post-exercise or heel-rise testing can be performed in patients with suspected PAD who have a normal ABI (see below), medial artery calcinosis reduces the sensitivity of post-exercise or heel-rise testing for diagnosing PAD [29].

Post-exercise ABI

Some patients with signs and/or symptoms of PAD have low normal or borderline ABI values (i.e., ABI values of 0.90–1.09), leaving uncertainty about the presence of PAD. In these patients, the ABI can be performed before and after treadmill exercise activity. A decline in ABI of 20% or greater after a treadmill exercise test indicates the presence of PAD [19, 30]. The ABI drops after exercise in patients with PAD because during lower extremity exercise, such as treadmill walking activity, systolic blood pressure values increase centrally, while arterial vessels that supply the lower extremities dilate. Together, these phenomena result in an increase in the brachial artery pressure simultaneously with a drop in the ankle pressure. These physiologic phenomena in response to exercise are observed even in healthy individuals. However, the magnitude of decline in the post-exercise ABI is approximately 5% in healthy people without lower extremity atherosclerosis vs. 20% in people with PAD [22]. A drop in a borderline ABI value (a borderline ABI value ranges from 0.90 to 1.09) of at least 20% after walking exercise is consistent with a diagnosis of PAD. Alternatively, a lower extremity pressure decline after exercise of >30 mm Hg can be used to diagnose PAD. In one study, the criterion of an ABI <0.90 after exercise or a >30 mm Hg drop in lower extremity pressure after exercise was 33% sensitive and 85% specific for PAD [32]. In a separate study, a recovery of the ABI to at least 90% of the baseline value within 3 min after completion of exercise was 94% specific for PAD [22].

The post-exercise ABI is typically measured before and after treadmill exercise in a vascular laboratory and requires treadmill equipment, and this testing may not be convenient in other settings. An alternative exercise ABI test is the heel-rise ABI, which does not require treadmill equipment and can be performed to elicit a diagnosis of PAD in people with borderline ABI values and suspected PAD. In the heel-rise ABI measurement, after the resting ABI, the patient lightly rests fingertips against a wall for balance, while rising up and down on the toes at a rate of one per second for 50 heel rises. The ABI is immediately repeated after the heel-rise exercise and has comparable sensitivity and specificity as a post-treadmill ABI for diagnosing PAD [30, 31]. Measuring the ABI as soon as possible after completion of the heel-rise exercise can improve the sensitivity of the post-heel-rise ABI for the diagnosis of PAD.

Using the ABI to Monitor Progression of Lower Extremity Atherosclerosis

An ABI decline of 0.15 is typically considered indicative of a clinically meaningful change in ABI [19, 33]. In one study of 349 patients with PAD identified from a vascular laboratory, rates of ABI decline >0.15 were 19% at 3 years follow-up and 37% at 5 years follow-up [34]. A separate study of 91 men with intermittent

claudication reported that an ABI decline of 0.15 or greater over a mean follow-up period of 2.5 years was associated with a 2.5-fold higher rate of revascularization and a 1.8-fold higher rate of symptom progression [35]. However, a study of 193 limbs in 114 patients with PAD showed a poor correlation between change in the ABI and progression of lower extremity atherosclerosis, measured by arteriogram or duplex scanning, over 3.3-year follow-up [33]. Of the 193 limbs, 72 (37%) showed meaningful progression of lower extremity atherosclerosis, measured by arteriography or duplex scanning during the 3.3-year follow-up period. During the same time period, an ABI decline of ≥0.15 was only 41% sensitive for lower extremity atherosclerotic disease progression, measured by arteriogram or duplex scanning [33]. This study suggested that the ABI is relatively insensitive in measuring progression of PAD. This relative insensitivity may be due to changes in lower extremity artery stiffening, such as medial artery calcinosis, as described above.

The ABI as a Prognostic Indicator of Cardiovascular Events and All-Cause Mortality

The ABI is an important prognostic indicator of risk for cardiovascular events and mortality. An association of ABI <0.90 with increased rates of cardiovascular events and all-cause mortality has been demonstrated consistently in epidemiologic population studies and among patients identified from clinical settings [3, 36–40]. These associations are independent of age, sex, race, cardiovascular risk factors, and comorbidities. In addition, lower ABI values are associated with greater risk of all-cause mortality (Fig. 2.2). This phenomenon was illustrated in a

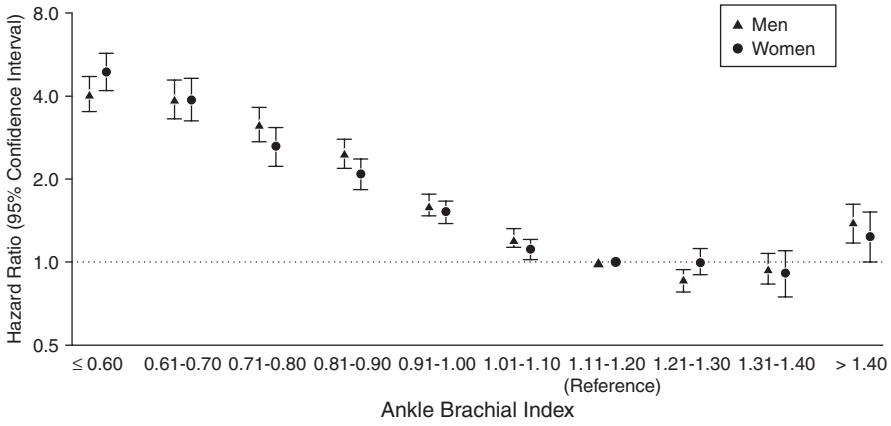


Fig. 2.2 Association of the ankle brachial index with all-cause mortality in men and women. (Reprinted with permission from Ankle Brachial Index Collaboration, Fowkes et al. [3])

meta-analysis of 16 population cohorts that included 24,955 men, 23,339 women, and 480,325 person years of follow-up. Mortality rates were 18.7% and 4.4%, respectively, in men with ABI <0.90 vs. men with ABI 1.10–1.40 [3]. Corresponding rates of mortality among women were 12.6% and 4.1%, respectively, in women with ABI <0.90 compared to those with ABI 1.10–1.40 [3]. Adjusting for the Framingham Risk Score, the hazard ratios for all-cause mortality were 2.9 (95% confidence interval (CI) = 2.3, 3.7) and 3.0 (95% CI = 2.0, 4.4) among men and women, respectively, with ABI <0.90 vs. ABI 1.10–1.40 [3]. When participants were categorized according to Framingham Risk Score (<10%, 10–19%, ≥20%), within each category of risk, an ABI <0.90 was associated with an approximately 2.0-fold increased risk of all-cause mortality, cardiovascular mortality, and rates of major coronary artery events, compared to the reference group of ABI 1.10–1.40. These results demonstrate that ABI <0.90 adds meaningfully to established cardiovascular risk factors as a predictor of all-cause mortality, cardiovascular mortality, and coronary event rates.

The Ankle Brachial Index as an Indicator of Subclinical Atherosclerosis in Other Vascular Beds

Low ABI values are also associated with an increased prevalence of subclinical atherosclerotic disease. For example, in the Multi-Ethnic Subclinical Atherosclerosis (MESA) study, the ABI was measured in 3458 and 3112 men who were free of clinically evident cardiovascular disease [41]. In this study, definite PAD was defined as an ABI <0.90, "borderline" PAD was defined as an ABI of 0.90–0.99, a low-normal ABI was defined as an ABI of 1.00–1.09, and absence of PAD was defined as an ABI of 1.00–1.03. ABI values <0.90 were associated with a higher prevalence of subclinical cardiovascular disease. For example, men with ABI <0.90 had significantly higher values for carotid artery intima media thickness and a higher odds ratio for presence of coronary calcium (odds ratio = 3.26) compared to men with a normal ABI (i.e., ABI of 1.00–1.30). Women with ABI <0.90 had a higher prevalence of coronary calcium (odds ratio = 2.85). Furthermore, men and women with borderline ABI values were more likely to have any coronary calcium than men and women with normal ABI values. Men with borderline ABI values also have higher carotid artery intima media thickness values compared to men with a normal ABI, and men with low-normal ABI values had significantly higher carotid intima media thickness values than men with normal ABI values. These results demonstrated that an ABI <0.90 is a marker of presence of subclinical atherosclerosis in people with no history of clinically evident cardiovascular disease. Even men and women with borderline ABI values and men with low-normal ABI values had higher prevalences of subclinical atherosclerosis compared to men and women with normal ABI values [41].

The ABI, Functional Impairment, and Functional Decline

Lower ABI values, indicative of more severe PAD, are associated with greater functional impairment, faster rates of functional decline, and higher rates of mobility loss in people with and without PAD. This was demonstrated in the Walking and Leg Circulation Study (WALCS), an observational longitudinal study of 460 men and women age 55 and older with PAD and 241 men and women age 55 and older without PAD who were well characterized, underwent baseline ABI and functional performance testing, and were followed longitudinally for up to 5 years [5–7]. Functional performance measures at baseline and annually included a 6-minute walk test and assessment, based on patient self-report, of the ability to walk ¼ mile and walk up and down a flight of stairs without assistance. At baseline, lower ABI values were associated with poorer 6-minute walk [5] (Fig. 2.3). Compared to

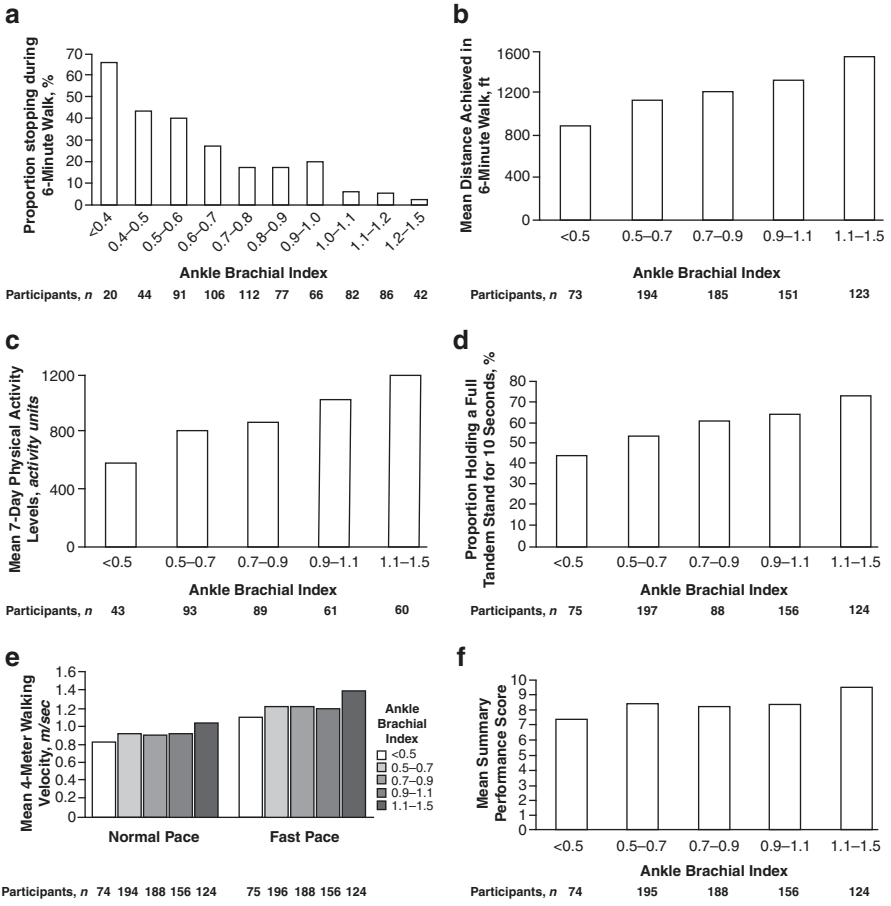


Fig. 2.3 Association of the ankle brachial index with the ability to walk continuously for 6 minutes without stopping

people with baseline ABI of 1.00–1.50, participants with an ABI <0.50 walked a shorter distance in the 6-min walk test (−515 ft (95% Confidence Interval −592 to −454), had poorer physical activity (−515 activity units (95% CI = −657 to −373), had slower 4-m walking velocity −0.21 m/s), and were significantly less likely to hold a full tandem stand (standing with one foot directly in front of the other) for 10 s (odds ratio 0.37 (95% CI = 0.18–0.76)). Lower ABI values were also associated independently with the inability to complete a 6-minute walk test without stopping to rest [5]. These associations were independent of potential confounders such as age, sex, race, smoking, body mass index, and comorbidities. At 2-year follow-up, among participants able to complete the 6-minute walk test without stopping at baseline, those with ABI <0.50, ABI 0.50–0.70, and ABI 0.70 to <0.90 were each significantly more likely to become unable to walk for 6 min continuously without stopping, compared to those with ABI of 1.10–1.50 at baseline [6]. These associations were also independent of potential confounders. At 5-year follow-up, among participants without baseline mobility impairment, lower ABI values were associated with significantly higher rates of mobility loss, with lower ABI values associated with progressively increased risk of mobility loss [7]. Those with ABI <0.50 at baseline had a 4.16-fold increased risk of mobility loss (95% CI = 1.58–10.92), and those with baseline ABI of 1.00–1.09 had a 2.61-fold increased risk (95% CI = 1.08–6.32) compared to those with a normal ABI at baseline [7]. In summary, lower ABI values are associated with greater functional impairment and higher rates of functional decline and mobility loss [5–7].

Limitations of the ABI

There are several limitations of ABI testing. First, the ABI is not sensitive to improvements in walking performance that occur in response to supervised exercise interventions. Although supervised treadmill exercise dramatically improves the 6-minute walk distance, the ABI value does not change concomitantly. Second, as indicated above, the ABI may not be sensitive to progression of lower extremity atherosclerosis. Third, the ABI is not a useful measure of the presence or severity of PAD in people with medial calcinosis of the lower extremity arteries. Despite these limitations, the noninvasive and inexpensive nature of the ABI, along with its generally high sensitivity and specificity for PAD, makes it a highly useful clinical diagnostic and prognostic tool.

Ankle Brachial Index Values in Women vs. Men and in Blacks vs. Whites

Women have lower ABI values on average than men, and black people have lower ABI values than whites. Among 1775 healthy people age 45–84 in the MESA cohort

with ABI values of 1.00–1.30 and no major risk factors for PAD (smoking, diabetes, dyslipidemia, hypertension), women were found to have an ABI value that was 0.02 lower than men, and blacks had an ABI value that was 0.02 lower than whites. While shorter height in women might explain an intrinsically lower ABI value in women compared to men, these results and similar findings from another study of sex differences in ABI showed that this difference in ABI value persisted even after adjusting for height [42, 43].

Conclusions

The ABI is an important noninvasive and inexpensive test that is reasonably sensitive and highly specific for detecting PAD and assessing PAD severity. The ABI is an important prognostic tool for risk of cardiovascular events and is associated with the degree of functional impairment and functional decline. However, the ABI may be falsely elevated by lower extremity medial calcinosis, which limits its utility for detecting PAD in people with diabetes and for detecting atherosclerotic disease progression in people with a low ABI.

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146–603. PMCID: PMC5408160.
2. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382(9901):1329–40.
3. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, de Backer G, Wautrecht JC, Kornitzer M, Newman AB, Cushman M, Sutton-Tyrrell K, Fowkes FG, Lee AJ, Price JF, d'Agostino RB, Murabito JM, Norman PE, Jamrozik K, Curb JD, Masaki KH, Rodríguez BL, Dekker JM, Bouter LM, Heine RJ, Nijpels G, Stehouwer CD, Ferrucci L, McDermott MM, Stoffers HE, Hooi JD, Knottnerus JA, Ogren M, Hedblad B, Witteman JC, Breteler MM, Hunink MG, Hofman A, Criqui MH, Langer RD, Fronek A, Hiatt WR, Hamman R, Resnick HE, Guralnik J, McDermott MM. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300(2):197–208. PMCID: PMC2932628.
4. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. Circ Res. 2015;116(9):1509–26.

5. McDermott MM, Greenland P, Liu K, Guralnik JM, Celic L, Criqui MH, Chan C, Martin GJ, Schneider J, Pearce WH, Taylor LM, Clark E. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. Ann Intern Med. 2002;136(12):873–83.
6. McDermott MM, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, Pearce WH, Schneider JR, Ferrucci L, Celic L, Taylor LM, Vonesh E, Martin GJ, Clark E. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. JAMA. 2004;292(4):453–61.
7. McDermott MM, Guralnik JM, Tian L, Liu K, Ferrucci L, Liao Y, Sharma L, Criqui MH. Associations of borderline and low normal ankle-brachial index values with functional decline at 5-year follow-up: the WALCS (The Walking and Leg Circulation Study). J Am Coll Cardiol. 2009;53(12):1056–62. PMCID: PMC3215766.
8. McDermott MM, Ferrucci L, Liu K, Guralnik JM, Tian L, Liao Y, Criqui MH. Leg symptom categories and rates of mobility decline in peripheral artery disease. J Am Geriatr Soc. 2010;58(7):1256–62. PMCID: PMC3227868.
9. McDermott MM, Fried L, Simonsick E, Ling S, Guralnik JM. Asymptomatic peripheral arterial disease is independently associated with impaired lower extremity functioning: the women's health and aging study. Circulation. 2000;101(9):1007–12.
10. McDermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, Chan C, Celic L, Pearce WH, Schneider JR, Sharma L, Clark E, Gibson D, Martin GJ. Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment. JAMA. 2001;286(13):1599–606.
11. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RAG, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME, Halperin JL. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135(12):e686–725. PMCID: PMC5479414.
12. McDermott MM, Ferrucci L, Tian L, Guralnik JM, Lloyd-Jones D, Kibbe MR, Polonsky TS, Domanchuk K, Stein JH, Zhao L, Taylor D, Skelly C, Pearce W, Perlman H, McCarthy W, Li L, Gao Y, Sufit R, Bloomfield CL, Criqui MH. Effect of granulocyte-macrophage colony-stimulating factor with or without supervised exercise on walking performance in patients with peripheral artery disease. JAMA. 2017;318(21):2089–98. PMCID: PMC5820720.
13. McDermott MM. Exercise rehabilitation for peripheral artery disease: a review. J Cardiopulm Rehabil Prev. 2018;38(2):63–9. PMCID: PMC5831500.
14. Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. Bull World Health Organ. 1962;27(6):645–58. PMCID: PMC2555832.
15. McDermott MM. Lower extremity manifestations of peripheral artery disease: the pathophysiologic and functional implications of leg ischemia. Circ Res. 2015;116(9):1540–50. PMCID: PMC4410164.
16. Newman AB, Naydeck BL, Sutton-Tyrrell K, Polak JF, Kuller LH, Cardiovascular Health Study Research Group. The role of comorbidity in the assessment of intermittent claudication in older adults. J Clin Epidemiol. 2001;54(3):294–300.
17. Criqui MH, Fronek A, Klauber MR, Barrett-Connor E, Gabriel S. The sensitivity, specificity, and predictive value of traditional clinical evaluation of peripheral arterial disease: results from noninvasive testing in a defined population. Circulation. 1985;71(3):516–22.
18. McDermott MM, Guralnik JM, Ferrucci L, Tian L, Liu K, Liao Y, Green D, Sufit R, Hoff F, Nishida T, Sharma L, Pearce WH, Schneider JR, Criqui MH. Asymptomatic peripheral arterial disease is associated with more adverse lower extremity characteristics than intermittent claudication. Circulation. 2008;117(19):2484–91. PMCID:PMC5077147.
19. Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, Fowkes FG, Hiatt WR, Jönsson B, Lacroix P, Marin B, McDermott MM, Norgren L, Pande RL, Preux PM,

Stoffers HE, Treat-Jacobson D, American Heart Association Council on Peripheral Vascular Disease, Council on Epidemiology and Prevention, Council on Clinical Cardiology, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126(24):2890–909.
20. Lijmer JG, Hunink MGM, van den Dungen JL, Smit AJ. ROC analyses of noninvasive tests for peripheral arterial disease. Ultrasound Med Biol. 1996;22(4):391–8.
21. Guo X, Li J, Paang W, Zhao M, Luo Y, Sun Y, Hu D. Sensitivity and specificity of ankle-brachial index for detecting angiographic stenosis of peripheral arteries. Circ J. 2008;72(4):605–10.
22. Ouriel K, McDonnell AE, Metz CE, Zarinss CK. Critical evaluation of stress testing in the diagnosis of peripheral vascular disease. Surgery. 1982;91(6):686–93.
23. McDermott MM, Criqui MH, Liu K, Guralnik JM, Greenland P, Martin GJ, Pearce W. Lower ankle/brachial index, as calculated by averaging the dorsalis pedis and posterior tibial pressure, and lower extremity functioning in peripheral arterial disease. J Vasc Surg. 2000;32(6):1164–71.
24. Nead KT, Cooke JP, Olin JW, Leeper NJ. Alternative ankle-brachial index method identifies additional at-risk individuals. J Am Coll Cardiol. 2013;62(6):553–9. PMCID:PMC3732795.
25. Hamalainen H, Ronnemaa T, Halonen JP, Toikka T. Factors predicting lower extremity amputation in patients with type 1 or type 2 diabetes mellitus: a population based 7-year follow-up study. J Intern Med. 1999;246(1):97–103.
26. Marston WA, Davies SW, Armstrong B, Farber MA, Mendes RC, Fulton JJ, Keagy BA. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. J Vasc Surg. 2006;44(1):108–14.
27. Tehan PE, Bray A, Chuter VH. Non-invasive vascular assessment in the foot with diabetes: sensitivity and specificity of the ankle brachial index, toe brachial index and continuous wave Doppler for detecting peripheral arterial disease. J Diabetes Complicat. 2016;30(1):155–60.
28. Brownrigg JR, Hinchliffe RJ, Apelqvist J, Boyko EJ, Fitridge R, Mills JL, Reekers J, Shearman CP, Zierler RE, Schaper NC, International Working Group on the Diabetic Foot. Effectiveness of bedside investigations to diagnose peripheral artery disease among people with diabetes mellitus: a systematic review. Diabetes Metab Res Rev. 2016;32:119–27.
29. Tehan PE, Barwick AL, Sebastian M, Chuter VH. Diagnostic accuracy of the postexercise ankle-brachial index for detecting peripheral artery disease in suspected claudicants with and without diabetes. Vasc Med. 2018;23(2):116–25.
30. McPhail IR, Spittel PC, Weston SA, Bailey KR. Intermittent claudication: an objective office-based assessment. J Am Coll Cardiol. 2001;37(5):1381–5.
31. Amirhamzeh MM, Chant HJ, Rees JL, Hands LJ, Powell RJ. Campbell WB.A comparative study of treadmill tests and heel raising exercise for peripheral arterial disease. Eur J Vasc Endovasc Surg. 1997;13(3):301–5.
32. Hoogeveen EK, Mackaay AJ, Beks PJ, Kostense PJ, Dekker JM, Heine RJ, Nijpels G, Rauwerda JA, Stehouwer CD. Evaluation of the one-minute exercise test to detect peripheral arterial disease. Eur J Clin Investig. 2008;38(5):290–5.
33. McLafferty RB, Moneta GL, Taylor LM Jr, Porter JM. Ability of ankle-brachial index to detect lower extremity atherosclerotic disease progression. Arch Surg. 1997;132(8):836–41.
34. Nicoloff AD, Taylor LM Jr, Sexton GJ, Schuff RA, Edwards JM, Yeager RA, Landry GJ, Moneta GL, Porter JM, Homocysteine and Progression of Atherosclerosis Study Investigators. Homocysteine and progression of atherosclerosis study investigators: relationship between site of initial symptoms and subsequent progression of disease in a prospective study of atherosclerosis progression in patients receiving long-term treatment for symptomatic peripheral arterial disease. J Vasc Surg. 2002;35(1):38–46.
35. Cronenwett JL, Warner KG, Zelencock GB, Whitehouse WM Jr, Graham LM, Lindenauer SM, Stanley JC. Intermittent claudication: current results of nonoperative management. Arch Surg. 1984;119(4):430–6.

36. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, Powe NR, Siscovick D. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. Arterioscler Thromb Vasc Biol. 1999;19(3):538–45.
37. Abbott RD, Petrovitch H, Rodriguez BL, Yano K, Schatz IJ, Popper JS, Masaki KH, Ross GW, Curb JD. Ankle/brachial blood pressure in men > 70 years of age and the risk of coronary heart disease. Am J Cardiol. 2000;86(3):280–4.
38. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, Howard BV. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation. 2004;109(6):733–9.
39. Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of the ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ. 1996;313(7070):1440–4. PMCID: PMC2352992.
40. Hooi JD, Kester AD, Stoffers HE, Rinkens PE, Knottnerus JA, van Ree JW. Asymptomatic peripheral arterial occlusive disease predicted cardiovascular morbidity and mortality in a 7-year follow-up study. J Clin Epidemiol. 2004;57(3):294–300.
41. McDermott MM, Liu K, Criqui MH, Ruth K, Goff D, Saaad MF, Wu C, Homma S, Sharrett R. Ankle-brachial index and subclinical cardiac and carotid disease. The multi-ethnic study of atherosclerosis. Am J Epidemiol. 2005;162(1):33–41.
42. Aboyans V, Criqui MH, McClelland RL, Allison MA, McDermott MM, Goff DC, Manolio TA. Intrinsic contribution of gender and ethnicity to normal ankle-brachial index values: The Multi-Ethnic Study of Atherosclerosis. J Vasc Surg. 2007;45(2):319–27.
43. Kapoor R, Ayers C, Visotcky A, Mason P, Kulinski J. Association of sex and height with a lower ankle brachial index in the general population. Vasc Med. 2018;23(6):534–40.