Screening for Peripheral Artery Disease and Cardiovascular Disease Risk Assessment With the Ankle-Brachial Index

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

**SUMMARY OF RECOMMENDATION AND EVIDENCE**

The US Preventive Services Task Force (USPSTF) concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for PAD and CVD risk with the ABI in asymptomatic adults (I statement) (Figure 1). See the Clinical Considerations section for suggestions for practice regarding the I statement.
Peripheral artery disease is a manifestation of atherosclerosis in the lower limbs. It can impair walking and, in severe cases, can lead to tissue loss, infection, and amputation. In addition to morbidity directly caused by PAD, patients with PAD are at increased risk for CVD events, because atherosclerosis is a systemic disease that also causes coronary and cerebrovascular events. The most recent data from the National Health and Nutrition Examination Survey (1999-2004) show that 5.9% of the US population 40 years or older has a low ABI (≤0.9), which indicates the presence of PAD. The true prevalence of PAD is difficult to establish, because more than half of persons with a low ABI are asymptomatic or have atypical symptoms and because population screening studies that use a gold standard diagnostic test are lacking.

Detection
The USPSTF found inadequate evidence on the accuracy of the ABI for identifying asymptomatic persons with PAD who can benefit from treatment.

Benefits of Early Detection and Intervention or Treatment
The USPSTF found inadequate evidence to assess whether screening for and treatment of PAD in asymptomatic patients leads to...
atherosclerosis. PAD treatment focuses on improving outcomes in symptomatic patients; interventions to prevent CVD events include smoking cessation, lowering cholesterol levels, managing high blood pressure, and antiplatelet therapy. If a low ABI indicates ankle-brachial index; CVD, cardiovascular disease; PAD, peripheral artery disease; USPSTF, US Preventive Services Task Force.

### Potential Preventable Burden

The true prevalence of PAD in the general population is not known. Data from the 1999-2004 National Health and Nutrition Examination Survey show that 5.9% of the US population 40 years or older (71 million adults) has a low ABI (<0.9), which may indicate the presence of PAD. The most recent prevalence data available are from a screening trial of Danish men aged 65 to 74 years, which identified a prevalence of 11% when PAD was defined as an ABI less than 0.9 or greater than 1.4. Two-thirds of identified patients reported no intermittent claudication, which is considered to be the classic symptom of PAD.

A 2016 systematic review found that over 5 years of follow-up, approximately 7% of patients with asymptomatic PAD developed intermittent claudication and approximately 21% of patients with intermittent claudication progressed to critical limb ischemia. In addition to the risk of worsening symptoms in the lower limbs, a low ABI is associated with increased risk of CVD events. Studies suggest that the 5-year cumulative incidence of cardiovascular mortality is 9% (95% CI, 7%-12%) in asymptomatic patients with a low ABI and 13% (95% CI, 9%-17%) in symptomatic patients with a low ABI; patients with a normal ABI had an average incidence of 5% (95% CI, 4%-6%).

### Potential Harms

Although minimal harms are associated with the ABI test, subsequent harms are possible. False-positive test results, false-negative test results, anxiety, labeling, and exposure to gadolinium or contrast dye from confirmatory MRA or CTA may occur, while further evaluation of CVD risk may involve stress testing or angiography. If the ABI is used to determine the need for pharmacologic treatment to reduce CVD risk, patients could receive additional treatment with...
resulting adverse effects or be reclassified to a lower risk category and potentially discontinue treatment that may be beneficial.4

Current Practice
An older study of US primary care practices found that 12% to 13% reported using the ABI for CVD screening weekly or monthly, 6% to 8% reported using it annually, and 68% reported never using it. However, the study was conducted more than a decade ago and may not reflect current practice.5

Assessment of Risk
In addition to older age, major risk factors for PAD include diabetes, current smoking, high blood pressure, high cholesterol levels, obesity, and physical inactivity, with current smoking and diabetes showing the strongest association.6 Although women have a slightly lower ABI compared with men, the prevalence of low ABI does not appear to vary significantly by sex after adjusting for age.6 Among healthy US men aged 40 to 75 years without a history of CVD, the risk for PAD over 25 years in the absence of 4 conventional cardiovascular risk factors (current smoking, high blood pressure, high cholesterol levels, or type 2 diabetes) is rare (9 cases per 100 000 men per year). These 4 risk factors account for 75% of all cases of PAD, and at least 1 of these risk factors is present at the time of PAD diagnosis in 96% of men.7

Screening Tests
Resting ABI is the most commonly used measurement for detection of PAD in clinical settings, although variation in measurement protocols may lead to differences in the ABI values obtained. Ankle-brachial index is calculated as the systolic blood pressure obtained at the ankle divided by the systolic blood pressure obtained at the brachial artery while the patient is lying down. A ratio of less than 1 (typically defined as <0.9) is considered abnormal and is commonly used to define PAD. Data on the accuracy of the ABI in asymptomatic populations are limited. One study of men and women older than 70 years reported that an ABI of less than 0.9 had a sensitivity of 15% to 20% and a specificity of 99% compared with whole-body MRA.8,9 Physical examination has low sensitivity for detecting mild PAD in asymptomatic persons.4 Although femoral bruit (vascular murmur at the femoral artery), pulse abnormalities, or ischemic skin changes significantly increase the likelihood ratio for low ABI (≤0.9), these signs indicate moderate to severe obstruction of blood flow or clinical disease.10 The clinical benefits and harms of screening for PAD with a physical examination have not been well evaluated, although such screening is often performed.4

Treatment and Interventions
Because PAD is a manifestation of systemic atherosclerosis in the lower limbs, treatment of PAD has 2 potential targets: reducing morbidity and mortality from lower limb ischemia and preventing CVD events due to systemic atherosclerosis. Treatment of PAD focuses on improving outcomes in symptomatic patients (eg, increasing walking distance and quality of life by improving symptoms of intermittent claudication and leg function, preventing or reducing limb complications, and preserving limb viability). Interventions to prevent CVD events include smoking cessation, lowering cholesterol levels, managing high blood pressure, and antiplatelet therapy. However, because the major risk factors for PAD are also used to calculate CVD risk, patients with a low ABI may already be recommended for these treatments.

Additional Approaches to Prevention
The USPSTF has made recommendations on many factors related to CVD prevention, including screening for high blood pressure,14 statin use,15 screening for diabetes,16 counseling on smoking cessation,17 counseling on healthful diet and physical activity,18 and CVD risk assessment with nontraditional risk factors.19 In addition, the USPSTF recommends use of low-dose aspirin by certain adults at increased risk for CVD.20

Other Considerations
Research Needs and Gaps
Large, population-based, randomized trials of screening vs no screening are needed to determine whether screening for PAD with the ABI improves clinical outcomes. One ongoing study in Denmark has published preliminary results; however, that study limited enrollment to men aged 65 to 74 years and included screening for abdominal aortic aneurysm and high blood pressure, making it difficult to evaluate the benefit of screening with the ABI alone.2 Two other ongoing trials that include the ABI as part of a screening bundle may have the same limitation.21,22 Future studies, in addition to isolating the effect of individual tests, should address the population of persons at potentially increased risk for PAD who are not already receiving interventions to reduce cardiovascular risk, because this is the population most likely to benefit from an additional screening intervention. Studies of screening with the ABI and interventions to stop disease progression in the lower limbs in more diverse populations (eg, women, racial/ethnic minorities, or persons with a lower socioeconomic status) and populations at high risk (ie, persons with diabetes) would also be valuable.

Discussion
Burden of Disease
The most recent data (1999-2004) show that 5.9% of US adults 40 years or older have a low ABI.1 In the United States, a low ABI (typically <0.9) is considered diagnostic for PAD in clinical practice, especially in the presence of symptoms. However, evidence that the ABI is an accurate screening test in asymptomatic adults is limited, so the actual prevalence of PAD is not known. When persons with known coronary artery disease or cerebrovascular disease are excluded, the reported prevalence of PAD in studies is 4.7%.1 Prevalence is higher in older populations; the prevalence of low ABI is 1.9% in adults aged 40 to 59 years, 8.1% in those aged 60 to 74 years, and 17.5% in those 75 years or older.23 However, the natural history of screen-detected PAD, including the development of morbidity and mortality directly related to atherosclerosis in the lower limbs, is not
well known. Therefore, the true burden of asymptomatic PAD is difficult to determine.

Scope of Review
To update its 2013 recommendation, the USPSTF reviewed the evidence on whether screening for PAD with the ABI in generally asymptomatic adults reduces morbidity or mortality from PAD or CVD. The current review expanded on the previous review to include persons with diabetes and interventions that include supervised exercise and physical therapy intended to improve outcomes in the lower limbs.4,24 The USPSTF also considered in a separate review whether the ABI improves CVD risk prediction when added to current risk assessment models (ie, Framingham Risk Score and the Pooled Cohort Equations).25

Accuracy of Screening Tests
In practice, low ABI is used as a surrogate marker for PAD; however, its accuracy as a screening tool for PAD in asymptomatic primary care populations has not been well studied. Only 1 fair-quality study evaluated the ABI as a screening test compared with a reference standard in a relevant population.29 That study was conducted in Sweden and included 306 participants, all of whom were aged 70 years at study entry. The mean interval between the ABI and the reference standard (whole-body MRA) was 16 months. The prevalence of PAD detected by MRA in the study population was relatively high at 28%. When whole-body MRA showing at least 50% stenosis in the pelvic or lower-limb arteries was used as the reference standard, an ABI of less than 0.9 had a sensitivity of 15% to 20% and a specificity of 99%. Because of its low sensitivity and high specificity, the positive and negative predictive values for the ABI in this study were 82% to 83% and 80% to 84%, respectively, depending on the leg. There were no subgroup analyses to examine whether accuracy results varied by subpopulation. The previous USPSTF review used evidence in asymptomatic adults to assess the potential accuracy of the ABI in asymptomatic patients; the current review did not reassess this literature. Although studies of test performance in symptomatic patients are helpful, asymptomatic patients may have less severe disease than symptomatic patients, so it is uncertain whether the sensitivity and specificity of the ABI found in studies of symptomatic patients would be applicable to asymptomatic patients.

Effectiveness of Early Detection and Treatment
The USPSTF found no population-based, randomized trials of the effect of PAD screening alone. One study, the Viborg Vascular (or VIVA) screening trial, assessed the effects of a screening bundle (combined screening for PAD, abdominal aortic aneurysm, and high blood pressure), reporting an absolute reduction in mortality of 0.006 (95% CI, 0.001-0.011) in the screening group at 5 years.26 However, the applicability of these results to screening for PAD in the United States is uncertain, given that the contribution of the individual tests was not measured and that screening for high blood pressure is supported by evidence-based guidelines in the United States, as is screening for abdominal aortic aneurysm in selected high-risk populations.

Four studies, 2 of aspirin therapy and 2 of exercise therapy, addressed treatment of asymptomatic patients with low ABI or PAD. Both aspirin studies were large, good-quality, randomized clinical trials (RCTs) that addressed whether asymptomatic men and women with low ABI (defined as ≤0.95 and ≤0.99, respectively) could benefit from daily aspirin therapy (100 mg/d). One study, Aspirin for Asymptomatic Atherosclerosis (N = 3350), enrolled men and women aged 50 to 75 years, with a mean follow-up of 8.2 years.27 The second study, the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial (N = 1276), enrolled patients 40 years or older with diabetes, with a median follow-up of 6.7 years.28 Neither study showed any significant difference in CVD events or mortality. Both studies reported no significant differences in development of intermittent claudication, and the POPADAD trial found no significant difference in PAD revascularization, bypass surgery, angioplasty, or amputation. In terms of subgroups analysis, there did not appear to be a difference in treatment effect based on age or sex.4

The 2 exercise studies were a small (N = 50), fair-quality US-based RCT with 12 weeks of follow-up29 and a good-quality Australian RCT (n = 882) with 1 year of follow-up.30 The intervention in both trials was a combination of risk factor modification and measures to increase physical activity. One-fourth of the participants in the US study and slightly more than half of the participants in the Australian study were asymptomatic. Both studies found no statistically significant differences in their primary outcome of walking distance or secondary outcomes of quality of life or self-reported symptoms, although the US study reported an improvement only in the mean stair climbing component of the Walking Impairment Questionnaire.29,30 There was no difference in development of PAD symptoms or improvement in quality of life. There was no evidence addressing whether subpopulations at greater risk for PAD had a differential treatment effect.

Potential Harms of Screening and Treatment
No studies directly addressed the harms of screening for PAD with the ABI. Harms resulting from testing may include false-positive test results (about 1%), false-negative test results (80% to 85%), exposure to gadolinium or contrast dye from confirmatory MRA or CTA, anxiety, labeling, and opportunity costs.4 The time and resources needed to screen with the ABI in a primary care setting may detract from other prevention activities that may have more benefit.

Two trials addressed the harms of aspirin treatment in asymptomatic persons. The Aspirin for Asymptomatic Atherosclerosis trial reported a nonsignificant trend toward increased major bleeding events requiring hospitalization in the aspirin therapy vs placebo group (hazard ratio, 1.71 [95% CI, 0.99-2.97]).27 The POPADAD trial reported a numerical decrease in hemorrhagic cerebrovascular accidents in the aspirin group, but the results were imprecise and not statistically significant.28 The 2 exercise trials did not report on harms.

Estimate of Magnitude of Net Benefit
The USPSTF found few data on the accuracy of the ABI for identifying asymptomatic persons who can benefit from treatment of PAD or CVD. Studies addressing the benefits of treating screen-detected patients with PAD are sparse; 2 good-quality studies showed no benefit of using the ABI to manage daily aspirin therapy in unselected populations, and 2 studies showed no benefit from exercise therapy. No studies addressed the harms of screening, although the potential exists for overdiagnosis, labeling, and opportunity costs. Studies that addressed the harms of treatment showed nonsignificant results. Therefore, the USPSTF concludes that the current evidence is insufficient and that the balance of benefits and
harms of screening for PAD with the ABI in asymptomatic adults cannot be determined.

**How Does Evidence Fit With Biological Understanding?**
Peripheral artery disease is generally considered a manifestation of systemic atherosclerosis. Detection when a patient is asymptomatic may suggest significant atherosclerosis in other vessels, such as the heart or brain, and patients may therefore be at risk for types of CVD other than PAD. Early detection and intervention to reduce atherosclerotic progression and prevent future CVD events could improve health outcomes compared with intervention strategies used in the absence of PAD screening. Patients with minimal or atypical symptoms may limit activity to avoid symptoms, leading to further deterioration. In this case, screening and treatment could theoretically prevent deterioration. However, a substantial number of asymptomatic persons with low ABI may never develop clinical signs or symptoms of CVD or PAD but would still be subjected to the harms of testing and subsequent treatments.

**Response to Public Comment**
A draft version of this recommendation statement was posted for public comment on the USPSTF website from January 16, 2018, to February 12, 2018. Several comments expressed concern that the USPSTF did not issue a separate positive recommendation for persons at higher risk of developing PAD. This population would include older adults and patients with diabetes, high blood pressure, high cholesterol levels, and current tobacco use. The USPSTF found the evidence addressing screening for PAD in high-risk, asymptomatic populations to be limited, with no compelling evidence to support differential screening or treatment in subpopulations at greater risk. In addition, patients in higher-risk groups (such as persons with diabetes and older adults) would likely already be candidates for interventions based on their global CVD risk, raising concern about the clinical significance of screening for additional risk factors (ie, asymptomatic PAD). The USPSTF added language to the “Accuracy of Screening Tests” and “Effectiveness of Early Detection and Treatment” sections to clarify this point.

Comments also raised concern that an I statement could have a negative effect on health care disparities for PAD. These comments cited evidence that the prevalence of PAD is disproportionately higher among racial/ethnic minorities and low-socioeconomic populations, and noted that the I statement could discourage testing and perpetuate disparities in treatment and outcomes. The USPSTF recognizes these well-established disparities in care. However, the evidence on screening and treatment in these groups is currently lacking, and the USPSTF was unable to determine the overall balance of benefits and harms. Future research should include diverse populations and report on their outcomes. The USPSTF added language to the “Research Needs and Gaps” section to clarify this point.

**Update of Previous USPSTF Recommendation**
This recommendation replaces the 2013 USPSTF recommendation. Although the USPSTF expanded its evidence review to include a broader population and range of interventions, the USPSTF’s recommendation remains an I statement.

**Recommendations of Others**
The American College of Cardiology and the American Heart Association released joint practice guidelines recommending screening with the ABI in patients at increased risk, including adults 65 years or older, adults 50 years or older with risk factors for atherosclerosis or a family history of PAD, and adults younger than 50 years with diabetes and 1 other risk factor for atherosclerosis. In 2015, the Society for Vascular Surgery recommended against screening with the ABI in adults in the absence of risk factors, history, signs, or symptoms of PAD; however, screening is considered reasonable in adults at higher risk (defined as age older than 70 years, current smoking, or diabetes; abnormal pulse examination; or other established CVD). In 2013, the American Academy of Family Physicians concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for PAD and CVD risk with the ABI in asymptomatic adults.

**ARTICLE INFORMATION**

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