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Ankle-Brachial Index Screening and Improving Peripheral Artery Disease Detection and Outcomes

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Lower extremity peripheral artery disease (PAD) affects an estimated 8.5 million adults in the United States and 202 million adults worldwide.[1,2] PAD consists of atherosclerosis of the lower extremity arteries, resulting in inadequate oxygen supply to lower extremity muscles during walking activity. People with PAD typically walk only 1 to 3 blocks before having to stop and rest because of ischemic leg symptoms. PAD is also a marker for the presence of atherosclerotic disease in the coronary and cerebrovascular arteries. Consistent with this phenomenon, people with PAD have higher rates of acute coronary events, ischemic stroke, and mortality, compared with people without PAD.

Related articles pages 177 and 184

Treatment goals for people with PAD consist of improving functional performance and preventing coronary events and stroke.[2] Supervised treadmill exercise and some home-based exercise interventions improve walking performance in PAD.[2,3] In randomized clinical trials, antithrombotic therapy and statins prevent cardiovascular events in people with symptomatic PAD.[2] Diagnosing PAD and implementing effective therapies has the potential to improve debilitating walking impairment and prevent cardiovascular events in millions of people with PAD.

Typically, PAD can be diagnosed relatively easily and noninvasively with the ankle-brachial index (ABI), a ratio of lower to upper extremity Doppler recorded systolic pressures. In the absence of PAD, arterial pressures increase with greater distance from the heart, because of increased arterial impedance as distal arteries taper. Therefore, systolic pressures are normally higher at the ankle than in the brachial arteries, and people without PAD have an ABI of 1.10 to 1.40. An ABI less than 0.90 is approximately 72% sensitive and nearly 99% specific for angiographically significant PAD.[4] People with ABI less than 0.90 have significantly higher rates of cardiovascular events, cardiovascular mortality, and all-cause mortality compared with those with a normal ABI, independently of cardiovascular disease risk factors.[5] An ABI less than 0.90 is also associated with greater functional impairment and higher rates of functional decline compared with normal ABI values.[6,7]

Intermittent claudication is the most classic symptom of PAD and consists of exertional calf pain that does not begin at rest and that resolves within 10 minutes of rest. Yet many people with PAD report leg symptoms that are not consistent with classic intermittent claudication.[6-8] Others report no exertional leg symptoms and are considered asymptomatic. Among people with an ABI less than 0.90, the prevalence of asymptomatic PAD varies from 20% to 60%, with lower prevalences of asymptomatic PAD in medical center settings and higher prevalences observed in communities outside of medical centers.[8] Among people with an ABI less

than 0.90, the prevalence of atypical leg symptoms ranges from 30% to 50%, with higher prevalences observed in patients with PAD who are identified in hospital settings or medical practices.[8]

Because most people with PAD do not have classic symptoms of intermittent claudication, the ABI is an important clinical tool for diagnosing PAD and identifying people at increased risk of cardiovascular events and functional decline. However, in this issue of *JAMA*, the US Preventive Services Task Force (USPSTF) Recommendation Statement concludes that current evidence is insufficient to recommend screening for PAD and cardiovascular risk with the ABI in asymptomatic adults (I statement).[9] This conclusion may appear counterintuitive, because the ABI is noninvasive, easily measured, sensitive for PAD, and identifies people with an ABI less than 0.90 at increased risk of cardiovascular events, mortality, and functional decline. Further evaluation of existing evidence helps to explain this recommendation.

First, the USPSTF decision applies specifically to using the ABI as a screening tool. By definition, "screening" refers to testing to detect disease in patients without signs or symptoms of disease. The USPSTF recommendation does not apply to people with ischemic symptoms during walking activity, who should be tested for PAD with the ABI.

Second, while antithrombotic therapy, statins, and angiotensin-converting enzyme inhibitors prevent cardiovascular events in people with PAD, evidence for these therapies comes from randomized trials enrolling people with established symptomatic PAD (based on claudication symptoms, lower extremity revascularization, or other criteria for symptomatic PAD) or clinically evident coronary artery disease or stroke. Recent randomized trials demonstrating benefits of evolocumab, vorapaxar, and low-dose rivoroxaban combined with aspirin to prevent progression of lower extremity atherosclerosis were also conducted in patients with established symptomatic PAD or other cardiovascular disease, and results may not apply to people with asymptomatic PAD who do not have clinically evident coronary or cerebrovascular disease.[10]

Third, evidence suggests that effective preventive therapies for patients with PAD may differ according to the presence vs absence of ischemic leg symptoms. Specifically, antithrombotic therapy did not reduce cardiovascular event rates in people with PAD who were asymptomatic, whereas clopidogrel, with or without aspirin, reduced cardiovascular event rates in patients with either symptomatic PAD or other symptomatic atherosclerotic disease.[10]

Fourth, although asymptomatic PAD is associated with significant functional impairment and functional decline,[6-8] limited data exist regarding interventions that improve walking performance in people with PAD who are asymptomatic. The recent Centers for Medicare & Medicaid Services decision to cover supervised exercise for PAD specifies that coverage applies to patients with PAD who have symptoms.

Two randomized trials demonstrated that aspirin did not prevent cardiovascular events in people with asymptomatic PAD.[11,12] For example, in 1 randomized trial, 28 980 asymptomatic men and women aged 50 to 75 years were screened with the ABI. The 3350 participants found to have an ABI less than 0.95 were randomized to receive either 100 mg of daily aspirin or placebo control. At 8.2-year follow-up, there was no difference in the primary end point of fatal or nonfatal coronary events, stroke, or revascularization (13.7 events vs 13.3 events per 1000 person-years).[11] These findings were consistent with another randomized trial of 1278 asymptomatic people with diabetes mellitus and a low ABI.[12]

An observational study in primary care medical practices from Catalonia reported that statin prescription in 2740 patients with asymptomatic PAD and no symptomatic cardiovascular disease was associated with lower cardiovascular event rates and all-cause mortality, compared with 2740 propensity-matched patients not started on statins (201/2740 [7.3%] vs 245/2740 [8.9%] for cardiovascular events and 263/2740 [9.6%] vs 316/2740 [11.5%] for all-cause mortality).[13] However, 72% of the patients in this study had a history of diabetes mellitus and already qualified for statin therapy even before the ABI measurement. Evidence suggests that the number of asymptomatic people with a low ABI and no other indication for cholesterol-lowering therapy is small.[13,14]

PAD is frequently undiagnosed, but many patients with undiagnosed PAD have exertional leg symptoms. One study tested 6979 patients from 350 primary care medical practices across the United States with the ABI. Included patients were either 70 years and older or aged 50 to 69 years with history of diabetes or stroke. Of the 6979 patients, 1865 (29%) had an ABI less than 0.90, including 823 without previously diagnosed PAD.[14] Of these previously undiagnosed patients with PAD, 42% had exertional leg symptoms that were atypical for claudication and 5% had classic symptoms of claudication. Even among patients with PAD reporting no leg symptoms, 40% developed ischemic leg symptoms during a 6-minute walk test.[7]

The following additional considerations should be noted. First, a recent cost-effectiveness analysis identified a cost-effectiveness ratio of $24 092 to $88 758 per quality-adjusted life-year for 1-time ABI screening.[15] However, this model assumed a 50% reduction in cardiovascular event rates, for which there is not definitive evidence for people who are asymptomatic and have an ABI less than 0.90. Second, given the relatively small number of asymptomatic people with an ABI less than 0.90 who do not already have another indication for cardiovascular preventive therapy and the relatively small number of cardiovascular events in these individuals,[11,13,14] a large expensive trial would be necessary to definitively test the utility of ABI screening in asymptomatic people. Third, the ABI is important for diagnosing nonspecific leg symptoms, common in older people at risk for PAD who frequently have comorbidities such as spinal stenosis, arthritis, and neuropathy that contribute to leg symptoms. But the USPSTF recommendation does not apply to these people.

The conclusions of the USPSTF should not be misconstrued as a determination that PAD is not common, clinically

important, or associated with significant adverse outcomes. Further research is needed to identify therapies that improve functional performance and prevent cardiovascular events in asymptomatic people with an ABI less than 0.90, which could provide sufficient evidence to support ABI screening in asymptomatic people. Until then, a careful history to identify ischemic leg symptoms in older people is likely to significantly improve PAD detection and treatment.

ARTICLE INFORMATION

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