The United States Preventive Services Task Force Recommendation Statement on Screening for Peripheral Arterial Disease

More Harm Than Benefit?

Joshua A. Beckman, MD, MS; Michael R. Jaff, DO; Mark A. Creager, MD

Abstract—Under the auspices of the Agency for Healthcare Research and Quality, the United States Preventive Services Task Force (USPSTF) recently released an update to its 1996 Peripheral Arterial Disease (PAD) Screening Recommendation Statement. The USPSTF recommended against PAD screening, giving the practice a “D” level recommendation. This level suggests that little or no benefit could accrue from PAD screening and that screening-associated harm could occur. The present commentary disputes the Task Force’s recommendation. The USPSTF statement omitted important peer-reviewed data on the prevalence, screening efficacy, and short-term adverse prognosis of patients with PAD and failed to consider the beneficial outcomes that probably would result from timely diagnosis and treatment of this important manifestation of atherosclerosis. The Task Force implied that screening may lead to unnecessary tests, including increased risk associated with use of contrast angiographic studies. However, most patients with PAD have neither classic symptoms of leg claudication nor threatened limbs but have an extraordinarily high rate of adverse cardiovascular events, such as myocardial infarction, stroke, and death—events that should serve as a key rationale for screening. Medical therapy, including risk factor modification and antiplatelet medications, is known to reduce cardiovascular morbidity and mortality rates in these patients. The Task Force’s recommendation against PAD detection may itself adversely result in inadequate recognition and treatment of PAD, with adverse public health consequences. We encourage the USPSTF to reevaluate the extant data, add vascular specialty expertise to its review group, and reconsider its recommendation. (Circulation. 2006;114:861-866.)

Key Words: peripheral vascular disease ■ diagnosis ■ tests ■ mortality ■ atherosclerosis

In December of 1999, the Healthcare Research and Quality Act of 1999 became law, reauthorizing the Agency for Healthcare Policy and Research with important modifications. First, the agency was renamed as the Agency for Healthcare Research and Quality (AHRQ), confirming its role as a scientific research agency. The addition of the word “quality” establishes AHRQ as the agency responsible for quality-of-care research. The goals of the agency are to“(1) meet the information needs of its customers—patients and clinicians, health system leaders, and policy makers—so that they can make more informed healthcare decisions; (2) build the evidence base for what works and what doesn’t work in healthcare and develop the information, tools, and strategies that decision-makers can use to make good decisions and provide high-quality healthcare based on evidence; and (3) develop scientific knowledge in these areas but . . . not mandate guidelines or standards for measuring quality.”

One method by which AHRQ carries out its mission is by issuing practice guidelines developed by the United States Preventive Services Task Force (USPSTF). As described on the AHRQ web site, “the USPSTF is the leading independent panel of private-sector experts in prevention and primary care. The USPSTF conducts rigorous, impartial assessments of the scientific evidence for the effectiveness of a broad range of clinical preventive services, including screening, counseling, and preventive medications. Its recommendations are considered the ‘gold standard’ for clinical preventive services.” In fact, “the mission of the USPSTF is to evaluate the benefits of individual services based on age, gender, and risk factors for disease; make recommendations about which preventive services should be incorporated routinely into primary medical care and for which populations; and identify a research agenda for clinical preventive care.” Thus, as the arm of the AHRQ responsible for the determination of appropriate clinical practice, interested in persuading patients, providers, and payers to adopt its recommendations, the influence of this agency is significant. It is in this
context that the recent USPSTF update of the “Recommendation Statement on Screening for Peripheral Arterial Disease (PAD)” is disappointing.

The USPSTF assigned routine screening of PAD a “D” recommendation, suggesting that the USPSTF minimally determined that PAD screening is ineffective or that the harm of testing outweighs the benefits. We suggest that a more complete review of the literature and careful evaluation would lead to a recommendation in favor of PAD screening. We present evidence that refutes the statement’s conclusion, providing a clinical framework that supports routine, office-based screening for PAD.

The USPSTF asks 5 Key Questions to determine the value of a PAD screening test. Specifically, they ask:

1. Does screening for PAD lead to reduced morbidity from PAD (including claudication, amputation, and impaired ambulation)?
2. What is the yield of screening (eg, prevalence, sensitivity, specificity) for PAD in primary care practice?
3. What are the harms of screening (eg, labeling, overtreatment)?
4. Does treatment of people with screening-detected PAD lead to improvement in the outcomes specified in Key Question 1 beyond the benefits of treatment at the time of symptoms?
5. What are the harms of earlier treatment for PAD (ie, side effects of treatment)?

USPSTF: Flawed Assumptions

The AHRQ staff and the Lewin Group (an independent, Virginia-based healthcare consulting firm) focused their review of the literature published since the last statement in 1996 on “direct evidence of decreased PAD-specific morbidity (improved health outcomes) from routine PAD screening, incremental benefits for patients (and subgroups) who received early treatment secondary to screen-detected PAD, and harms from PAD screening.” The definition of screening in medicine is “the examination of a group of usually asymptomatic individuals to detect those with a high probability of having a given disease, typically by means of an inexpensive diagnostic test.”

The implicit goal of the USPSTF statement is to determine whether detection of PAD in asymptomatic patients—persons who feel well—will improve how their legs feel. We agree that screening an asymptomatic population is not likely to improve PAD-specific morbidity (claudication and amputation). Nevertheless, the scope of the review avoids the most important unfavorable outcome faced by all individuals with PAD: the marked increase in short-term risk of adverse cardiovascular events, including myocardial infarction, stroke, and death. PAD is caused by atherosclerosis, a systemic disorder, and these patients often have undiagnosed coronary and cerebrovascular disease. The diagnosis of PAD can be established easily by measuring the ankle-brachial index (ABI), a simple, low-cost, reliable, and risk-free noninvasive test that relates the ankle systolic blood pressure to the brachial artery systolic blood pressure, with an approximate sensitivity of 79% to 95% and specificity of 95% to 100%.

PAD screening should occur because of the potential benefit to life and limb. A reasonable analogy to ABI screening would be targeted screening for an occult malignancy, such as mammography or colonoscopy, yet use of the ABI probably would be more beneficial, less costly, and associated with less risk than these accepted screening interventions. As a result of the risk to life conferred by undiagnosed PAD, in both asymptomatic and symptomatic individuals, the American College of Cardiology/American Heart Association Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic), written in collaboration by the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, and the Society for Vascular Medicine and Biology, reports that “individuals with asymptomatic lower extremity PAD should be identified by examination and/or measurement of the ankle-brachial index (ABI) so that therapeutic interventions known to diminish their increased risk of myocardial infarction (MI), stroke, and death may be offered”—a Class I indication.

Evidence of High Diagnostic Yield in Targeted Primary Care Screening

The prevalence of PAD was approximated by the USPSTF, using the estimate in the American Heart Association Facts and Figures. For Key Question 2, the USPSTF reports no new evidence on the yield of screening (prevalence) in primary care patients. The epidemiology of PAD and prevalence of PAD patients seen by primary care physicians has been clarified by 3 recent large studies, not one of which was cited by the USPSTF. In the Peripheral Arterial Disease Detection, Awareness, and Treatment in Primary Care (PARTNERS) study, screening was performed prospectively in 350 primary care offices across the United States. Patients who were ≥70 years of age or persons aged 50 to 69 years with a history of cigarette smoking or diabetes were screened by an ABI in the physician’s office. Of the 6979 subjects who were screened, PAD was detected in 29%. Among those with PAD, 44% had PAD alone without other significant manifestations of atherosclerosis. It is important to note that patients with PAD were less well treated with risk factor—modification therapies than were patients with other forms of atherosclerosis. In the German Epidemiological Trial on Ankle Brachial Index (GETABI study), 344 primary care practitioners across Germany screened 6880 consecutive patients 65 years or older. PAD was found in 19.8% of men and 16.8% of women. Finally, in the National Health and Nutrition Examination Survey
Figure: Range of Estimated Mortality Reduction in Targeted PAD Screening

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<th>7 Yr Mortality</th>
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<th>Lives Saved</th>
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Range of estimated mortality rate reduction in targeted PAD screening. Estimates are made on the basis of published data for prevalence (PARTNERS STUDY7), 7-year mortality rate (adjusted) (Cardiovascular Health Study,26 Limburg PAOD study,16 Saskatchewan Health Study,28 and Rotterdam Study27), and mortality rate reductions with appropriate therapy (Rotterdam Study25). Mortality rate reductions provided range from 25% to 50% to account for possible use of beneficial therapies for other risk factors or atherosclerosis in the population to be treated.

(NHANES), 1999 to 2000, of 2174 free-living persons, the prevalence of PAD in the United States was estimated at 5 million persons, with 14.5% of the population >70 years of age affected.9 Each of these studies makes clear that PAD is common in primary care practice and that the diagnosis is easily established by use of the ABI in well-defined populations. These studies, among many others, effectively rebut the USPSTF statement about the data that were readily available for review, as they concluded that “no new evidence . . . was identified” for Key Question 2.

Whereas we agree that, like any arbitrary testing strategy, indiscriminate PAD screening would be unlikely to provide benefit, we support targeted PAD screening for high-risk patients (defined as individuals <50 years of age with diabetes and one other atherosclerosis risk factor; individuals 50 to 69 years of age with a history of smoking or diabetes; individuals ≥70 years of age; those with leg symptoms with exertion (suggestive of claudication) or ischemic rest pain; and those with an abnormal lower-extremity pulse examination), as recommended by the American College of Cardiology/American Heart Association PAD Guidelines.4

More interesting, perhaps, is the contention by the USPSTF that “nearly 75% of those with PAD are asymptomatic” and the lack of attention that point receives. In the PARTNERS study described above, 10% of the PAD population had classic claudication (symptoms of muscular ischemia brought on by walking). However, 50% of the PAD subjects had other leg symptoms, a finding that has been reported in all PAD surveys. The prevalence of arthritis, lumbar spine disease, and venous insufficiency is high in these age groups and may either contribute to functional disability or obscure a patient’s description of leg ischemic symptoms. PAD patients with atypical leg symptoms also have impaired walking ability when compared with patients without PAD.10 However, atypical leg symptoms do not now lead to prompt ABI testing. On the basis of observational data, approximately 10% of the Medicare population with PAD would be undiagnosed. In fact, nearly 90% of all PAD patients would be missed if ABI testing were withheld from patients without classic symptoms and those with atypical leg symptoms.

The most important omission of the USPSTF statement, however, is the failure to incorporate the increased risk of cardiovascular death in its report. Because it is impossible to reduce limb morbidity in patients who have not complained of symptoms, most vascular disease experts recommend the generalized screening of patients for PAD because of the increased risk of death and the evidence supporting the use of medical therapies to reduce adverse outcomes.11 Twenty years ago, Widmer and Biland12 reported a 37% mortality rate at 11 years in patients with PAD. Epidemiological studies have demonstrated a strong relation between decreasing ABI and death.13,14 Even asymptomatic patients with PAD have 10-year mortality rates as high as 40%.15 In the Limburg Peripheral Arterial Occlusive Disease Study, the 7-year mortality rate was 10.9% in patients without PAD, compared with 25.8% in patients with asymptomatic PAD and 31.2% in those with symptoms.16 Indeed, in a systematic review of the literature that included studies that used an ABI cutoff between 0.80 and 0.90 to classify patients with PAD, followed patients prospectively, and recorded cardiovascular outcomes, the presence of a low ABI more than doubled the risk of coronary heart disease, more than doubled the risk of stroke, and more than quintupled the risk of cardiovascular death.17 Thus, absence of symptoms neither defines a “risk-free” population nor results in freedom from cardiovascular events.

Rationale for Screening: Ischemic Event Reduction

It is puzzling that the USPSTF decided to apply a standard different from the one they used in the recent abdominal aortic aneurysm screening guidelines.18 In that guideline, the possibility of saving one life for every 500 screened patients over a period of 5 years in the absence of an effect on total mortality was enough to grant screening in asymptomatic male smokers age 65 to 75 years a grade “B” recommendation. The misconception underlying the difference in approach to screening between abdominal aortic aneurysms and PAD relates to the flawed concept of “early” PAD. The leg vasculature is very well collateralized, such that the amount of atherosclerosis required to reduce perfusion pressure is substantial. Reductions in perfusion pressure require an extensive burden of atherosclerosis. It is the systemic nature of atherosclerosis that confers the increase in cardiovascular risk to these patients. Indeed, risk of death is strongly correlated with the ABI and extent of atherosclerosis.14 Thus, the decision by the USPSTF to consider only morbid outcomes for PAD but mortal outcomes for aortic aneurysmal disease is inconsistent and directly contributes to a flawed PAD update.
In our opinion, the principal goal of screening for PAD is not to improve walking distance in patients whose symptoms are minimal or absent but rather to reduce the risk of major cardiovascular morbidity and mortality. The USPSTF fails to consider the data demonstrating that atherosclerotic risk–modifying therapies reduce mortality rates in patients with PAD. The USPSTF acknowledges the importance of smoking cessation and states "... counseling for smoking cessation ... should be offered to all patients who smoke, regardless of the presence of PAD." This statement indicates misunderstanding of the time course of risk, which is distinctly different between the general population and individuals with PAD. In an era in which access to tobacco cessation resources is constrained and the benefits of treatment could be amplified, identification of high-risk groups is merited. In addition, for Key Question 4, the USPSTF found only one cross-sectional study to demonstrate the benefits of statin treatment for asymptomatic individuals with PAD. The Task Force also stated that there was no association with the outcome measures and other treatments, such as aspirin or angiotensin-converting enzyme (ACE) inhibitors. The recently published Heart Protection Study confirmed the benefits of cholesterol lowering in patients with PAD. Before this study, and amplified by these study results, the National Cholesterol Education Program guidelines from the Adult Treatment Panel III declared that the PAD-associated ischemic event risk is equivalent to the risk associated with coronary artery disease and therefore requires aggressive reduction in total and low-density lipoprotein cholesterol. Patients with PAD require reduction in low-density lipoprotein cholesterol similar to patients with coronary heart disease, a goal that is not required for a patient without known atherosclerosis. This mandate is also now included in the peer-reviewed PAD Guidelines. The Task Force makes no mention of the need for reduction in blood pressure to goal levels as established by the Joint National Committee VII Report. A prospective, multicenter, randomized trial found that modification of the renin–angiotensin system with an ACE inhibitor ameliorates the major cardiovascular events among patients with PAD. The use of antiplatelet therapy is a cornerstone of therapy for patients with established atherosclerosis. Compelling evidence indicates that antiplatelet therapy reduces adverse cardiovascular events such as myocardial infarction, stroke, and death in patients with PAD.

An important unanswered question is the potential benefit of screening in terms of effectiveness (Figure). Three parameters shape the potential benefits of screening: disease prevalence, event rates, and the benefit accrued with therapy. The first parameter has been well defined by the PARTNERS and other related cross-sectional studies: For every 100 patients ≥70 years of age or between 50 and 69 years of age who smoke or have diabetes, 29 patients will have PAD. The second parameter has been defined by several large epidemiological studies. In the 4 most recent large studies, PAD mortality rates range from 3.9% to 8.2% per year. Recently, Feringa and colleagues have reported the efficacy of cardioprotective pharmaco-therapies in 2420 patients with PAD to provide insight into the third parameter. Over a median follow-up period of 8 years, 44% of the cohort died. In multivariate analysis adjusted for all baseline clinical variables, use of a statin reduced mortality rates by 54%, use of a β-adrenergic blocker reduced mortality rates by 32%, use of aspirin reduced mortality rates by 28%, and use of an ACE inhibitor reduced mortality rates by 20%. Thus, according to the estimates noted above, the approximate reduction in mortality rates may range from 2 to 9 lives saved per 100 patients screened over the course of 7 years of follow-up, assuming a 25% to 50% mortality rate reduction with the institution of appropriate therapy (Figure). In contrast, the USPSTF estimated that screening in men 65 to 74 years of age who smoked >100 cigarettes in their lifetimes would save 1 life for every 500 patients screened over a period of 5 years. It becomes hard to reconcile the abdominal aortic aneurysm and PAD USPSTF statements with a direct comparison of potential benefit. The establishment of the diagnosis of PAD in asymptomatic patients and institution of appropriate therapies should offer reductions in cardiovascular morbidity and mortality and a conclusion opposite to that reported by the USPSTF in Key Question 4.

Rationale for Screening: Symptomatic Improvement

Screening of symptomatic patients may result in institution of therapy that can improve limb function and limb ischemic symptoms. It is now documented that most patients with PAD have substantial functional limitations that reduce walking distance and speed even if they do not have classic claudication. Individuals with claudication have an impairment of quality of life that is at least as great as that produced by other cardiovascular diseases. Detection of disease permits treatment. Supervised exercise programs result in meaningful improvement in physical functioning. Moreover, the United States Food and Drug Administration has approved cilostazol as therapy to improve the symptoms of intermittent claudication, and many patients have gained significant benefit from this. Percutaneous and surgical revascularization is recommended for patients with lifestyle-limiting intermittent claudication and critical limb ischemia. Screening asymptomatic patients with atypical presentations probably would result in improved PAD-specific functional outcomes.

PAD as a Cardiovascular Public Health Priority

The USPSTF suggests that a screening program may result in “harm.” The USPSTF defines harm as “false-positive results and unnecessary work-ups.” Inexpensive diagnostic tests, such as the ABI, are sufficient to confirm the diagnosis of PAD. Vascular specialists do not recommend invasive angiographic testing to confirm PAD in any care guideline. Anatomic definition by angiography is pursued only when the patient has advanced leg symptoms, maximal medical therapy has failed to relieve symptoms, and the patient requires revascularization. In the recent multispecialty PAD guidelines, use of duplex ultrasound, computed tomographic angiography, magnetic resonance angiography, and contrast angiography is only recommended to define vascular anato-
my in individuals who are anticipated to undergo revascularization—not to establish the PAD diagnosis.4 The practice of evidence-based medicine should eliminate the unnecessary use of anatomic imaging, averting the potential harm in screening. Indeed, patients who are informed about the implications of PAD will understand the need for aggressive, cost-effective medical interventions that can prolong life and diminish disease progression to the more advanced stages that might require revascularization.

The National Institutes of Health, through the National Heart, Lung, and Blood Institute, has undertaken several initiatives that underscore the importance of diagnosis and management of vascular diseases, especially PAD. First, it has sponsored clinical research grants in PAD.32 Second, it has created funding opportunities to increase the number of training programs for specialists in this area.33 Finally, it is partnering with a coalition of more than 40 specialty professional societies and health advocacy groups, the PAD Coalition (www.padcoalition.org), to create a national public awareness campaign to increase the national appreciation of the risks of PAD.34 Each of these initiatives recognizes the central fact of PAD in the United States and internationally: It is underappreciated, underdiagnosed, and undertreated.

Conclusion
It is our hope that a more thorough and thoughtful review of the existing literature will convince the USPSTF that its position is potentially harmful to a large and growing population of Americans whose lives and functional independence are at risk in the short term. We recognize that a randomized, prospective trial is the only sure method to answer this question definitively. However, on the basis of the best available evidence, we believe that routine, targeted screening for PAD would increase the frequency of diagnosis, improve the use of recommended medical therapies, and reduce cardiovascular morbidity and mortality rates. This approach is not harmful and would serve to protect cardiovascular public health. We suggest the addition of vascular specialty expertise to the USPSTF review of PAD. A revision of the current position should be undertaken to address strategies to reduce the risk of adverse cardiovascular events in this high-risk population.

Disclosures
None.

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