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American Heart Association | American Stroke Association

April 15, 2013

Robert Cosby, MD
USPSTF
540 Gaither Road
Rockville, MD 20850

Re: Screening for Peripheral Artery Disease and CVD Risk Assessment

Dear Dr. Cosby:

On behalf of the American Heart Association (AHA), including the American Stroke Association (ASA) and more than 20 million AHA and ASA volunteers and supporters, we appreciate the opportunity to submit our comments in response to the U.S. Preventive Services Task Force draft recommendation statement on Screening for Peripheral Artery Disease and Cardiovascular Risk Assessment with Ankle Brachial Index. As explained in this letter, the AHA recommends the following:

- Confine the recommendation for ABI screening of asymptomatic adults to those at high cardiovascular risk such as older adults (65 years of age or greater).
- Include the additional literature that supports the value of ABI screening, in addition to measurement of traditional risk factors.
- Change the grade recommendation to "B", consistent with definition of this rating and the PAD guidelines promulgated by the AHA.

Since 2005, with the creation of the first multispecialty guidelines document in peripheral artery disease,[1] the AHA has recommended a single measurement of the ankle-brachial index to detect patients with the coronary heart disease risk equivalent, peripheral artery disease,[2] in order to provide well-established cardiovascular risk reduction therapies to reduce death, myocardial infarction, and stroke in patients over the age of 65 years and patients who smoke or have diabetes older than 50 years. This recommendation was reaffirmed in 2011[3] and again in 2012.[4]

In contrast, the U.S. Preventive Services Task Force provided a 'D' recommendation in 2005 suggesting performance of the ABI may cause harm because of "false positive results and unnecessary work-ups".[5] As noted by the current draft report, the 2005 review was very limited, focusing only on lower extremity symptoms and function. It did not address PAD as a predictor for CVD.

As a result, the current evidence review was meant to re-evaluate this work and provide a full review of ABI screening and cardiovascular disease outcomes. Based on this more thorough evaluation, the current review concludes with the following: "The U.S. Preventive Services Task Force (USPSTF) concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for peripheral artery disease (PAD) and cardiovascular disease (CVD) risk assessment with ankle brachial index (ABI) in adults."

AHA has a critical interest in peripheral artery disease, risk factor modification, and cardiovascular risk reduction and we would like to provide our thoughts on why AHA's recommendations differ from those of the USPSTF, and why we believe the current USPSTF draft recommendation and draft evidence review are problematic, and if published in its current form, would adversely affect an opportunity to reduce the risk of cardiovascular events of the American public, particularly those millions of patients with undiscovered and untreated PAD.[6]

Draft Evidence Review

The Task Force requested the answer to three questions concerning the draft evidence report, two of which provide insight into how the differences in the AHA and USPSTF recommendations occurred. The first question for review posed by the Task Force is "Do you think this report includes all of the relevant studies?" The authors of the draft evidence review independently reviewed 4,434 abstracts and 418 articles. However, many key articles weren't included in the analysis, because the Task Force "excluded studies whose subjects primarily had known intermittent claudication. The Task Force also excluded studies conducted exclusively in persons with known CVD, diabetes, or severe chronic kidney disease (stage 4 and 5). [The Task Force] excluded studies conducted in hospital or specialty settings (i.e., vascular clinics or vascular labs) as these settings typically represented populations selected for known or highly suspected PAD. Because we focus on largely asymptomatic persons, our primary outcomes of interest are CVD events and risk factor reduction, rather than lower extremity symptoms." AHA does not think this report includes all relevant studies. Indeed, the exclusion of studies in hospital and specialty settings, in particular, artificially narrows the literature base and limits the Task Force's ability to assess the questions it poses.

The logic for excluding studies that are likely to include high risk patients, such as those conducted in hospitals and specialty clinics is flawed, since these often include older persons and those with cardiovascular risk factors who are at greatest risk for PAD. Studies published within the last several years have demonstrated a strong relationship between ABI and cardiovascular outcomes, even after controlling for components of the Framingham Risk Score[7] or for FRS and more risk factors.[8,9] The Task Force assumes these symptomatic and/or high risk patients are already under appropriate risk factor management but provides no evidence for this assumption. In fact, the opposite has been demonstrated in the literature. Indeed, based on these data, governmental authorities in the United States,[2] United Kingdom,[10] and Canada[11] each have stated that PAD, unrelated to leg symptom status, is a coronary heart disease risk equivalent deserving of secondary prevention level therapy. The AHA is concerned that limiting the data set in this artificial manner will result in excess morbidity and mortality for patients with PAD.

The second question posed is "Do you agree with how the included studies and the overall evidence have been interpreted?" We disagree and will answer this question in relation to the key questions posed by the Task Force. The Task Force developed six key questions regarding ABI measurement in adults. We are concerned that the answers to the six key questions regarding ABI measurement in adults

are significantly influenced by the limitation of the evidence base used in this analysis and the subjective interpretation of its analyses. Of these, key question 2 is "What is the diagnostic accuracy of ABI as a screening test for PAD in generally asymptomatic adults?" The Task Force used one relatively small study, PIVUS, which used MRA as a gold standard to detect PAD. MRA detects specific locations of stenosis, whereas the ABI provides an integrated summation of lower extremity PAD. The diagnosis of PAD by the ABI signifies the accrual of atherosclerosis sufficient to reduce perfusion pressure to <90% of that in the brachial artery when measured at rest. Thus, the ABI is a *summative* value that integrates all of the lower extremity occlusive disease, while MRA is an *anatomic* test that identifies individual plaque severity (and the MRA is an expensive test that is not appropriate for population screening). Moreover, excluding other studies that have examined high risk and symptomatic populations, which are included in the AHA recommendations, substantially weakens the Task Force's ability to assess the accuracy of the ABI in detecting PAD. This topic has been reviewed in great detail by the AHA and the ABI is as accurate as other screening tests recommended by the Task Force including blood pressure and mammography. The AHA has reviewed the ABI measurement methods and diagnostic accuracy in great detail[4] and found an overall diagnostic ability area under the curve of 0.87 to 0.95. The single study cited by the Task Force misrepresents the diagnostic accuracy of the test. Furthermore, there is no plausible biologic reason that the overall accuracy of the ABI measurement should differ between asymptomatic individuals from the community and those with documented PAD in a hospital or medical center setting.

To address key question 3, "What are the harms of screening with ABI?", neither evidenced-based literature nor evidence derived from CMS claims data are presented to suggest that unnecessary anatomic testing may result from ABI screening. Moreover, inclusion of potential harms must be balanced by inclusion of potential benefits. For example, patients misclassified with PAD could be started on statin therapy. Two meta-analyses have demonstrated statin-therapy related mortality reductions in patients without atherosclerosis or diabetes, so benefit may accrue.[12,13]

Key question 4 is "Does ABI accurately predict CVD morbidity and mortality independent of traditional risk factors?" This question forms the crux of the analysis and the central issue of the recommendation. Three flaws undermine the analysis by the Task Force for this key question. First, the review states, "Data from multiple population cohort studies (18 cohorts) show that low ABI (0.9 or less) is generally associated with future CAD and CVD events, independent of FRS factors." The use of the word <u>generally</u> implies that the ABI usually or for the most part is associated with future cardiovascular events. This is a subjective judgment and mischaracterization of the evidence. In <u>all</u> studies of 1,000 or more subjects (as noted by the Task Force in Appendix D), the ABI is strongly correlated with cardiovascular outcomes. Second, the authors exclude large, epidemiologically valid, prospectively collected outcome studies in PAD for not controlling statistically for Framingham Risk Factors found in the NCEP ATP III report (sex, age, total cholesterol, HDL, active smoking, and hypertension or its treatment). Two examples demonstrate inappropriate exclusion of important confirmatory and consistent work that clarify outcomes in the group of interest: patients with asymptomatic PAD. In the German Epidemiological Trial on Ankle Brachial Index (getABI) observational cohort study of 6,880 primary care patients, subjects with PAD diagnosed based on ABI had markedly increased cardiovascular hazard compared to those without PAD.[9] This was true when limited to subjects with asymptomatic PAD. This was also true when the outcomes were controlled for sex, history of atherosclerotic events, diabetes, age, smoking, homocysteine, hypertension, BMI, and lipid disorders. Thus, the getABI studied controlled outcomes for *more* factors and still found an association, yet was excluded in the evidence review. Similarly, in the Limburg Peripheral Arterial Occlusive Disease study

of 3,649 subjects followed for 7.2 years, for the subjects with PAD (diagnosed by low ABI), the hazard ratio for nonfatal MI for patients with asymptomatic PAD was 1.6 for cardiovascular disease, 1.6 for coronary heart disease, 1.7 for nonfatal myocardial infarction, 2.1 for cerebrovascular disease, and 1.4 for total mortality, while adjusting for age, sex, smoking, hypertension, diabetes, hypercholesterolemia, and baseline other cardiovascular disease.[8] Thus, even when controlled for more factors than FRS, these important studies are not considered.

The evidence review committee also provides a review of the net reclassification index (NRI) of the ABI over the Framingham Risk Score (FRS) among a variety of studies and concludes that "that the overall NRI is relatively small, although may be higher among older persons." Having reviewed the methods in detail, we will not argue the statistical methods by which NRI was computed in the various studies. However, the Task Force has provided a *subjective* assessment of an objective value. This value judgment forms the crux of the 'I' recommendation, and as such requires heightened scrutiny. Indeed, two criteria must be made clear: 1) is the NRI computed for ABI screening different from other tests routinely used in this arena and 2) is the NRI computed for the ABI lower than that found in other Task Force recommended preventive services. We believe the value judgments placed on the results are inconsistent with the other tests used in clinical practice and other recommendations of the USPSTF. The NRI calculated among the varying studies for the ABI is indistinguishable from risk factors commonly used and recommended in clinical practice to clarify the risk of coronary heart disease. Pencina and colleagues demonstrated that the addition of HDL to the other FRS variables has an NRI of 0.06,[14] the same value that the ABI has beyond FRS including HDL. Thus, the evidence review committee is giving inadequate weight to the ABI when compared to cardiovascular tests recommended for CVD risk assessment by the Task Force. Moreover, clinicians routinely use and CMS reimburses tests with this level of NRI. Examples include positron emission tomography myocardial perfusion scanning for atypical chest pain[15] or the addition of family history and hs-CRP to the Framingham Risk Score.[16] Also, other risk stratification services are recommended by the Task Force with smaller NRIs than that computed for the ABI. For example, the Task Force recommends colorectal cancer screening, which has never been shown to reduce all-cause mortality and requires a minimum of a decade to reduce death from colorectal cancer. Similarly, the Task Force recommends a single screening for AAA which reduces aneurysm-related but not all-cause mortality. Finally, the Task Force recommends biennial mammography for women aged 50 to 75 years, despite no effect on all-cause mortality and the need to test 1,339 women aged 50 – 59 years to prevent one breast cancer death in 10 years.

Finally, although we understand and support testing the value of ABI screening when added to the Framingham Risk Score, the Task Force should recognize that this requirement does not reflect primary care practice in the United States. When studied, scoring systems are used by fewer than 1 in 5 primary care physicians.[17] As a result of routine clinical practice, the vast majority of patients with PAD do not get life-prolonging therapies. Based on work from the NHANES data base, 5 million of the estimated 7 million Americans with PAD are not taking a statin, 5.4 million are not taking an ACE inhibitor or ARB, and 4.5 million are not taking an antiplatelet agent.[6] Indeed, the de facto state of care for the millions of patients with PAD in the United States is poor and easily amenable to life-saving therapies with generic medications. The Task Force acknowledged the systemic nature of atherosclerosis and the increased rate of cardiovascular morbidity and mortality in patients with PAD. The AHA recommends that the Task Force acknowledge the state of care for patients with PAD when providing a value judgment of the ABI.

Key question 5 is "Does treatment of asymptomatic or minimally symptomatic adults with PAD lead to improvement in patient outcomes beyond the benefits of treatment in symptomatic adults, or beyond the benefits of treatment of adults with known CVD risk factors (i.e., smoking, hypertension, hyperlipidemia)?" The Task Force "excluded seven trials for quality and 77 studies because the majority of patients had intermittent claudication. No trials examined the benefit of earlier (while asymptomatic) versus later (while symptomatic) treatment of PAD." The AHA understands that the question pertains to the value of screening patients without leg symptoms, but there is no evidence that the presence of leg muscle symptoms has any impact on stabilization of coronary and cerebrovascular conduit artery atherosclerotic plaque. The deliberate exclusion of patients with intermittent claudication as a means to prove that treatment of patients with asymptomatic PAD would benefit from anti-atherosclerotic therapies violates the principles of medical treatment in every condition associated with atherosclerosis: medical personnel do not wait for cardiovascular symptoms to develop in patients with diabetes, hypertension, dyslipidemia, or aortic aneurysm. The initiation of statin therapy in the Heart Protection Study in patients with PAD reduced the absolute rate of major vascular events by 6% over 5 years.[18] This includes an absolute reduction of 1.8% in all cause mortality. Ramipril, in the HOPE study,[19] reduced the rate of CV mortality, MI, and stroke by 5 to 6% and all-cause mortality by 6% over 4.5 years of follow up in the PAD patients specifically. The implication that the presence or absence of exercise-related leg muscle symptoms may be determinative of the cardiovascular effects of statins or ACE inhibitors is belied by distinct origin of leg skeletal muscle ischemic pain and coronary heart or cerebrovascular atherosclerotic plaque progression or rupture. Thus, the AHA believes that exclusion of seminal trials including Heart Protection Study and HOPE is arbitrary and fosters a conclusion inappropriate to the evidence currently available.

Because the Task Force sets the standard of practice for primary care physicians, one point needs clarification. The authors report that "The ABI may take up to 15 minutes to measure and likely cannot be conducted as part of the primary care visit." The authors make two errors here. First, there is no reason that an ABI, performed for cardiovascular risk assessment, needs to be made on more than one occasion for the vast majority of subjects. The rate of change of the ABI is slow, such that significant changes may be noted over the course of 4 to 5 years.[20,21] Thus, the AHA recommends a single screening for patients 65 years and older. Moreover, once diagnosed, leg-based therapies are determined by symptom complex, not ABI, so repeat ABIs do not factor into decision-making. Second, the technique for blood pressure measurement advocated by the USPSTF requires just a slightly shorter amount of time (including the premeasurement rest period)[22] and is required *at least annually*. The exclusion of one measurement on the basis of time (ABI) and the retention of the measurement of blood pressure with a similarly required time is arbitrary and lacks objective foundation.

The AHA believes that ABI screening of patients aged 65 years and older provides a reliable NRI with a high likelihood of benefit when appropriate therapy is employed. This is reflected in our published recommendations:

- The resting ABI should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD, defined as individuals with 1 or more of the following: exertional leg symptoms, nonhealing wounds, age 65 and older, or 50 years and older with a history of smoking or diabetes (Class 1; LOE: B).[23]
- The ABI can be used to provide incremental information beyond standard risk scores in predicting future cardiovascular events (Class IIa; LOE A).[4]

- Individuals with an ABI ≤0.90 or ≥1.40 should be considered at increased risk of cardiovascular events and mortality independently of the presence of symptoms of PAD and other cardiovascular risk factors (Class I; LOE A).[4]

Summary

This evidence review represents an outlier beyond standard medical practice in the United States,[1] NICE guidelines from the United Kingdom,[10] and Canada.[11] The methodology is flawed yielding a faulty and subjective conclusion. In particular, the exclusion of studies that include high risk patients in the determination of ABI accuracy and the value of cardiovascular risk reduction is inappropriate. Finally, the demonstrated NRI matches that used in current practice and its interpretation by this Task Force implies a subjective assessment that effectively results in different recommendations for screening for PAD then other diseases such as colon or breast cancer.

AHA Recommendation

It is the view of the AHA that a single ABI screening should receive a B recommendation from the USPSTF for men and women aged 65 years and older. As has been described in the 2005 Multispecialty Guideline Document and reaffirmed in the 2011 update, screening patients one time for PAD would increase the general welfare by improving medical therapy and reducing CVD, thus meeting the definition of a Task Force 'B' recommendation: *There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.* We make this statement because in the absence of screening, there are millions of patients with PAD not treated with appropriate therapies and have a higher mortality rate.[6] If we have any hope of achieving the American Heart Association's 2020 impact goals for CV Health[24] or the United States Department of Health and Human Services' Healthy People 2020 objectives or the Million Hearts Initiative, we must continue to look for and deal with PAD in our nation's seniors.

If you have any questions, please do not hesitate to contact Dr. Rose Marie Robertson, MD, AHA's Chief Science Officer at rosemarie.robertson@heart.org.

Sincerely,

Donna K. Arnett

Donna K. Arnett, PhD
President, American Heart Association

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