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COLLEGE of
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USPSTF Coordinator
c/o USPSTF
5600 Fishers Lane
Rockville, MD 20857

Dear Sir or Madam:

Thank you for the opportunity to comment on the Draft Evidence Review and the Draft Recommendation Statement for Peripheral Artery Disease and Cardiovascular Disease: Screening and Risk Assessment with the Ankle Brachial Index.

As we have expressed in previous communications to the U.S. Preventive Services Task Force (USPSTF), we appreciate the Task Force's decision to update the recommendation for peripheral artery disease (PAD) screening. However, we have serious concerns with the draft evidence review, because the report does not include all of the relevant studies. We also disagree with the Task Force's decision to develop one recommendation statement that applies to the entire adult asymptomatic population. We believe it would be more appropriate to focus the evidence review and the recommendation statement on the population most at-risk for PAD, including adults aged 65 years and older and those with risk factors. If the Task Force narrows its recommendation to that population, or creates a second recommendation statement focused on that population, the evidence would support an "A" grade.

We discuss these concerns and our recommendations in more detail below.

DRAFT EVIDENCE REVIEW

In the request for comments, the Task Force asks whether the draft evidence report includes all of the relevant studies. As noted above, we believe the answer is no. For example, since the USPSTF conducted its last review of this recommendation in 2013, the results of a PAD/abdominal aortic aneurysm screening trial have been published, which show that the screening results in reduced mortality. Choosing not to include this study, while including two others that improperly define PAD, may have adversely impacted the evidence review and the resulting recommendation statement.

Studies Excluded from the Evidence Review

As part of its review of Key Question 1 (**Is Screening for PAD in Generally Asymptomatic Adults with the ABI Effective in Reducing CVD or PAD Morbidity or Mortality?**), the Task Force suggests that no randomized trials of PAD screening were identified, and that the Viborg Vascular trial is multicomponent and therefore disqualified. In the recommendation statement, the following is asserted, “The USPSTF found no population-based, randomized trials of the effect of PAD screening. One study, the Viborg Vascular (or VIVA) screening trial, assessed the effects of a screening bundle (screening for PAD, abdominal aortic aneurysm, and high blood pressure), reporting an absolute reduction in mortality of 0.006 (95% CI, 0.001 to 0.011) in the screening arm at 5 years. 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 standard care in the United States, as is screening for abdominal aortic aneurysm in selected high-risk populations.” In the Systematic Review, the Task Force notes, “Applicability of such findings to the U.S. population are called into question because: 1) hypertension screening and management are standard practice and occur at a lower diagnostic threshold than used in the trial; 2) AAA screening in ever-smoking men in this age group is already recommended (although variably implemented); and 3) nearly all participants would have 10 percent or greater 10-year ASCVD risk based on age and male sex alone, they would be candidates for consideration of statins or aspirin already.”

We do not understand why the USPSTF excluded this trial, especially since the Task Force has previously expressed an active interest in the publication of it. In the USPSTF's 2013 evidence review, the Task Force noted that “Although the evidence base we reviewed was limited, screening and risk prediction using the ABI is an active field of research”.¹ Indeed, the report went on to specifically cite the VIVA trial: “The Viborg Vascular screening trial, which is currently under way, is a population-based screening trial that is randomly assigning 50,000 men aged 65 to 74 years to screening for PAD and abdominal aortic aneurysm versus no screening. Primary outcome data, including all-cause and CVD mortality, should be available in late 2018” and cite the study's study protocol paper.² It is unclear how the Task Force's opinion inverted from thinking this study would help inform a future PAD recommendation, to deciding this study should be excluded from the most recent review. The details of the study, including any “problems” that led to its exclusion, were fully known by the Task Force during the 2013 review.

Worse, the exclusion of the VIVA trial and the arguments supporting the exclusion are not supported by the evidence and appear arbitrary. First, the supposition that hypertension screening does not occur in Denmark is incorrect. Indeed, the Danish follow the WHO standards with a goal of reducing blood pressure to below 140 / 90 mm Hg, the same as in the United States until the recent AHA/ACC guidelines. Indeed, the Danish do a similar job at finding hypertension, as the rates of knowledge of diagnosis (72%), treatment (64%), and treatment to control (57%) demonstrate.³ Second, limiting the screening to higher blood pressures to insure accuracy for the trial biased the study towards the null by making sure that most patients with high blood pressure would be missed and not treated. Third, it is, by definition, impossible to perform an ABI screening study without also obtaining blood

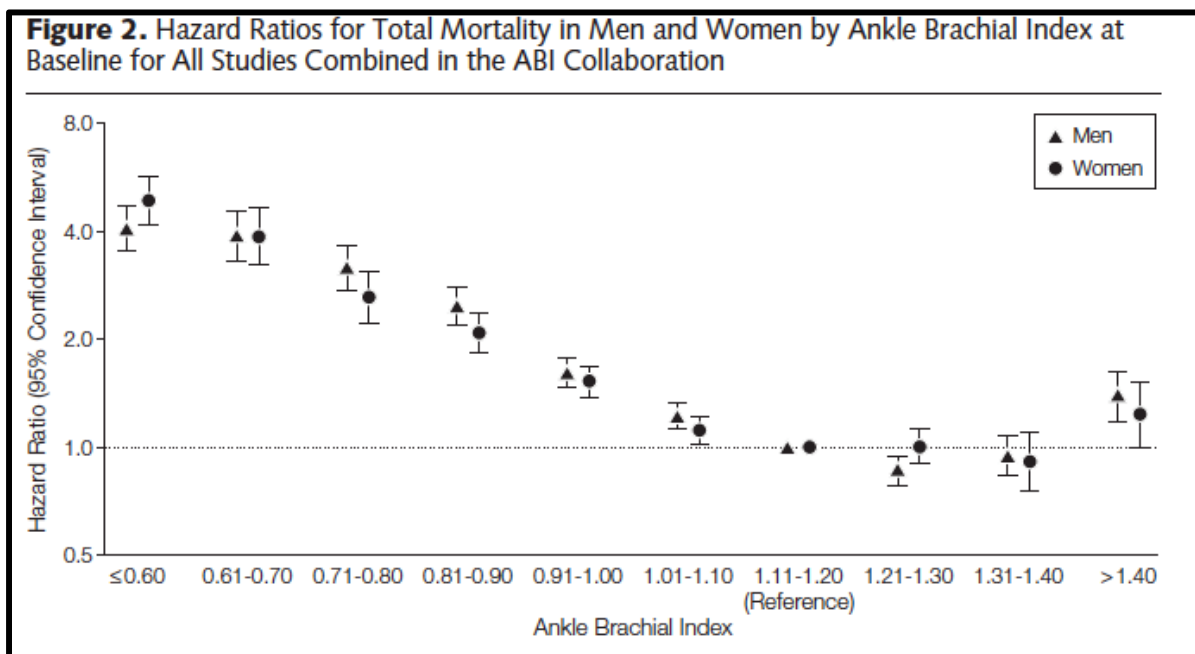
pressure. Excluding the benefit of finding a second disease moves the goal posts in a way to make every ABI screening study impossible. As awareness of hypertension remains an area requiring improvement in the United States; an added benefit of ABI screening study would be improved hypertension awareness and supports the stated goals of the Task Force in its screening for hypertension document. Furthermore, the VIVA trial authors reported that the exclusion of subjects who benefitted from the initiation of antihypertensive therapy, the overall benefit reduced modestly, raising the hazard ratio from 0.93 to 0.94. Thus, the contribution of hypertension diagnosis and treatment did not drive the benefit and the complaint that screening for hypertension may “muddy the waters” is not substantiated by the investigators. Fourth, it is quite easy to separate the effect of AAA screening. There were 67 deaths attributable to AAA during the study, 15 fewer in the screened group. There were 149 fewer deaths due to all causes in the invited group compared to the control group, thus, ~90% of the death reduction was not AAA-related and AAA-screening alone required more than a decade of follow up to demonstrate a modest mortality benefit. Fifth, ABI screening reduced in-patient total days for PAD by 19% and ischemic heart disease by 11% both compared to the control group. It is difficult to understand how the Task Force could conclude that the contribution of screening for PAD was unclear when both PAD morbidity and cardiovascular mortality are reduced in this important trial.

Finally, and perhaps most convincingly, the Task Force has already set a standard for which other screening modalities have been deemed beneficial. This screening program meets that threshold easily. The number needed to invite to prevent one death at 4.4 years was 169 persons. The number needed to invite to prevent one death at 10 years from breast cancer using biennial mammography for women aged 50 to 59 years is 1,339 persons. The number needed to screen (a less stringent threshold) to prevent one colorectal cancer death at 10 years for fecal occult blood testing is 1,176 persons. There are no randomized trials for colonoscopy, yet it is a recommended screening modality. The number needed to invite for AAA alone ranges from 352 to 667 persons to prevent one death. The addition of a single ABI screen in this age group saves lives more efficiently than any of the fully recommended services above. Any recommendation besides “A” or “B” suggests an arbitrary assignment of benefit and may unintentionally communicate inconsistency across disease states. We believe that patients with PAD deserve the same chance at prolonging life as those with other conditions. This month, Krist and colleagues, for the Task Force, defined preventive services as “intended for those without signs or symptoms to improve the quality and/or length of life”.⁴ It is unclear how the Task Force can conclude that PAD screening does not meet this goal.

Using the ABI to Diagnose PAD

The Draft Evidence Review and Draft Recommendation Statement appear to misrepresent PAD and how it is diagnosed, including in its assessment of Key Question 2 (**What Is the Diagnostic Accuracy of the ABI as a Screening Test for PAD in Generally Asymptomatic Adults?**) We are concerned that these errors significantly diminish the validity of the analysis and the Task Force’s recommendation.

For example, in the opening paragraph of the Evidence Review, the Task Force does not integrate the concept of atherosclerotic burden into the diagnosis. The review states, “While the term “abnormal ABI” is often used interchangeably with “PAD” in clinical practice and research, this review will differentiate an abnormal ABI from PAD diagnosed by a confirmatory imaging study (i.e., digital subtraction angiography {DSA}, computed tomography angiography,⁵ magnetic resonance angiography {MRA}, and duplex ultrasound).” There are two problems with this statement. First, the diagnosis of PAD is not made by the presence or absence of atherosclerosis as may be detected by anatomic studies such as those listed above. PAD gains its salience when the amount or burden of atherosclerosis in the lower extremities is sufficient to reduce ankle perfusion pressure. Many studies have shown that as the ABI decreases, the rate of adverse cardiovascular events increases. This relationship demonstrating the importance of atherosclerotic burden was most clearly demonstrated by the Ankle Brachial Index Collaboration (reference 38 in the systematic review). This collaboration examined 16 cohorts and, during 480,325 person-years of follow up, the risk of death by ABI increased linearly (see figure below).⁶ Thus, the key determinant of adverse outcomes is not presence/absence on imaging, but severity of flow limitation. Moreover, the selection of 0.90 for the diagnosis of PAD is quite conservative, as the risk of total and cardiovascular mortality rises by more than 50% once the ABI is less than 1.0. Furthermore, it is estimated that 60-70% of patients with a high ABI (> 1.3-1.4) have reduced tissue perfusion and as noted above are at increased risk.



The second error concerns the method of diagnosis. The Task Force defines PAD thusly, “Patients with confirmed PAD diagnosed by a confirmatory imaging study (e.g., DSA, CTA, MRA).” That is not the accepted definition of diagnosis by all specialties in medicine, the federal government, and concerned lay organizations. In the 2016 AHA/ACC Guideline on

the Management of Patients with Lower Extremity PAD,⁷ developed in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation, Inter-Society Consensus for the Management of Peripheral Arterial Disease, Society for Cardiovascular Angiography and Interventions, Society for Clinical Vascular Surgery, Society of Interventional Radiology, Society for Vascular Medicine, Society for Vascular Nursing, Society for Vascular Surgery, and Vascular and Endovascular Surgery Society, the resting ABI is 1) recommended to establish the diagnosis and 2) reported as abnormal when the ABI is ≤ 0.9 . The Guideline then addresses the use of CTA, MRA, and angiography stating specifically that these modalities are “useful to diagnose anatomic location and severity of stenosis for patients with symptomatic PAD in whom revascularization is considered.” These imaging modalities are used by all medical specialists for procedural planning and are not considered appropriate for diagnosis.

Federal governmental agencies also define PAD with an ABI. The Centers for Medicare and Medicaid Services recently approved coverage for supervised exercise therapy for patients with symptomatic PAD. In the May 25, 2017 Decision Memo, CMS states that “The diagnosis of PAD can be confirmed through the ankle-brachial index (ABI), which is the ratio of systolic pressure at the ankle to that in the arm, or the toe-brachial index for patients where ABI is not reliable due to noncompressible vessels, common for patients of advanced age or chronic diabetes. ABI results of 0.91 to 0.99 are considered borderline, with an ABI of 0.90 or less considered abnormal.” In the last 20 years, the Food and Drug Administration has approved five medications for patients with PAD: clopidogrel, simvastatin, ramipril, cilostazol, and vorapaxar. In not one of the studies supporting approval of these medications was DSA, CTA, or MRA used as a diagnostic modality. For each study, patients either had previous revascularization for symptomatic PAD or reduced ABI. The Centers for Disease Control and Prevention, in its description of PAD, similarly suggests that the ABI is the first test to be used to diagnose PAD.

In addition, lay organizations that represent the population at risk report that the ABI is the method to diagnose PAD. AARP, for example, in its Health Encyclopedia, tells its 37 million members that “Your doctor can use the ankle-brachial index to diagnose PAD, which compares the blood pressure in your arm to the blood pressure in your ankle. If the blood pressure in your ankle is lower than the pressure in your arm, you may have PAD.”

The use of anatomic imaging by the Task Force as the reference standard for PAD diagnosis is a misunderstanding of the nature of the disease and is out of step with the medical community. Using this definition artificially constricts the evidence base and skews the Task Force’s conclusions inappropriately. An imaging-based diagnostic algorithm for PAD would also raise costs of screening and could lead to unnecessary lower extremity revascularization procedures as has been pointed out by the Task Force in previous evaluations of the ABI.

Finally, it appears in the discussion about the ABI, that the Task Force is holding ABI screening to a higher standard than other previously recommended screening tests. The review reports that “it is important to note that an abnormal ABI is not diagnostic for PAD because resting ABI is a screening test that does not have 100 percent sensitivity and

specificity.” This is a standard not required for any other screening service. None of the recommended services that received an “A” or “B” Grade, including AAA screening, bacteriuria screening in pregnant women, blood pressure screening, breast cancer screening, cervical cancer screening, colorectal cancer screening, depression screening, gestational diabetes screening, intimate partner violence screening, obesity screening, or tuberculosis screening has 100% sensitivity and specificity. It is unclear if the Task Force intends to adopt this – test perfection – as the new standard moving forward.

Measuring the Harms of ABI Screening

We are concerned that multiple standards of evidence are being applied for the assessment of benefits and harms as a result of ABI testing. In Key Question 3 (**What Are the Harms of Screening for PAD With the ABI?**), the Task Force describes a single vasovagal event prior to contrast injection for MRA. This is not a harm of ABI screening. There is no harm to this testing modality.

Measuring the Impact on Health Outcomes

We also have concerns with Key Question 4 (**Does Treatment of Screen-Detected or Generally Asymptomatic Adults with PAD or an Abnormal ABI Lead to Improved Patient Health Outcomes?**) and the Task Force’s decision to include two aspirin studies that identify individuals as having PAD even though they do not meet the standard diagnostic criteria.

These two trials are seriously limited and do not provide evidence in support or against screening for PAD. The inclusion criteria for patients in the Aspirin for Asymptomatic Atherosclerosis (AAA) trial did not identify patients with PAD. As the authors state, “The ABI was calculated as ratio of the *lowest* ankle pressure (lower of posterior tibial and dorsalis pedis and of left and right) to the higher pressure of either arm. Those with an ABI of 0.95 or lower were entered into the trial”.⁸ Standard diagnostic criteria, as outlined by the Task Force, is to use the higher pressure with a threshold of ≤ 0.9 . The method used in this trial identified a low risk group with a 10-year risk of MI, stroke, and CV death of 8.2% -- below the threshold that the Task Force would suggest the use of aspirin or a statin. This is not a PAD population.

The Prevention and Progression of Arterial Disease and Diabetes (POPADAD) trial studied patients with diabetes and PAD, however, the ankle brachial index threshold was 0.99, not the standard 0.90.⁹ The impact of this decision becomes clear in two ways: 1) the mean ABI was 0.9, suggesting that half of the study participants did not have PAD and 2) the trend towards benefit with aspirin therapy in patients with an ABI of ≤ 0.9 . Thus, the inclusion of patients without PAD likely reduced the overall detectable benefit in this trial.

An additional flaw in this Key Question, is the strawman of asymptomatic PAD. As acknowledged in the systematic review, the relationship between leg symptoms and heart attack / stroke is not substantiated by the literature. The Task Force confirms that there is no important link between symptoms and cardiovascular outcomes by describing the GetABI trial¹⁰ (reference 40 in the systematic review). The review notes that, “An analysis of 6,880

unselected adults age 65 years or older in Germany showed that among those with PAD, the risk of a composite of all-cause death, MI, and CVA was not statistically significantly different for those with and without symptoms.” Moreover, the Task Force endorses the importance of leg symptoms for the prediction of limb outcomes by going on to comment, “However, risk of a composite outcome additionally including lower-extremity peripheral vascular events or any revascularization was statistically significantly higher in those with symptoms (HR 1.48 {95% CI, 1.21 to 1.80}). This composite outcome was driven by peripheral revascularizations, which may have been triggered by symptoms. The presence of PAD conferred high risk for cardiovascular events or all-cause mortality, regardless of symptoms, when compared with adults with no PAD.” This data has been reconfirmed recently in the EUCLID trial.¹¹ In this trial comparing clopidogrel and ticagrelor in 13,885 patients with PAD, there was no difference in the primary composite outcome of CV death, MI, and stroke between the subjects recruited based on a low ABI vs those recruited with a history of limb revascularization. In contrast, enrollment for symptoms significantly increased the risk of acute limb ischemia. Leg symptoms well predict leg events while the low ABI well predicts CV events. Thus, it is irrational to exclude treatments currently FDA-approved for patients with PAD. Clopidogrel, simvastatin, ramipril, and vorapaxar are all approved to reduce cardiovascular events in patients with PAD – whether or not they have symptoms.

DRAFT RECOMMENDATION STATEMENT

As mentioned above, we are also disappointed by the Task Force’s decision to develop one recommendation statement that applies to the entire asymptomatic adult population. We believe this is a significant mistake that will cause harm to patients with undiagnosed PAD. Instead, the screening recommendation should focus on adults who are at high risk of PAD, including adults aged 65 years and older, as demonstrated by the VIVA trial, and those with risk factors.

Numerous independently funded, population-based studies have demonstrated that PAD prevalence increases with age. This evidence base demonstrates that PAD is very efficiently detected in individuals over 65 years, and this diagnosis has a major beneficial impact for Americans who do not have prior evidence of atherosclerosis.

If the Task Force were to focus on this narrower patient population, the evidence clearly supports an “A” grade.

There are numerous examples of the Task Force developing age-specific recommendations, including screening for impaired visual acuity screening in older adults, breast cancer, abnormal blood glucose and type 2 diabetes mellitus, abdominal aortic aneurysm, dental caries in children, lung cancer, hearing loss in older adults, osteoporosis, colorectal cancer, and lipid disorders in adults.

We do not understand why the Task Force did not choose to treat ABI screening for PAD in a similar matter. The evidence base clearly demonstrates that the prevalence of PAD increases with age. Therefore, we urge the USPSTF to revise its draft recommendation statement to focus on the population most at-risk for the disease, based on age and risk

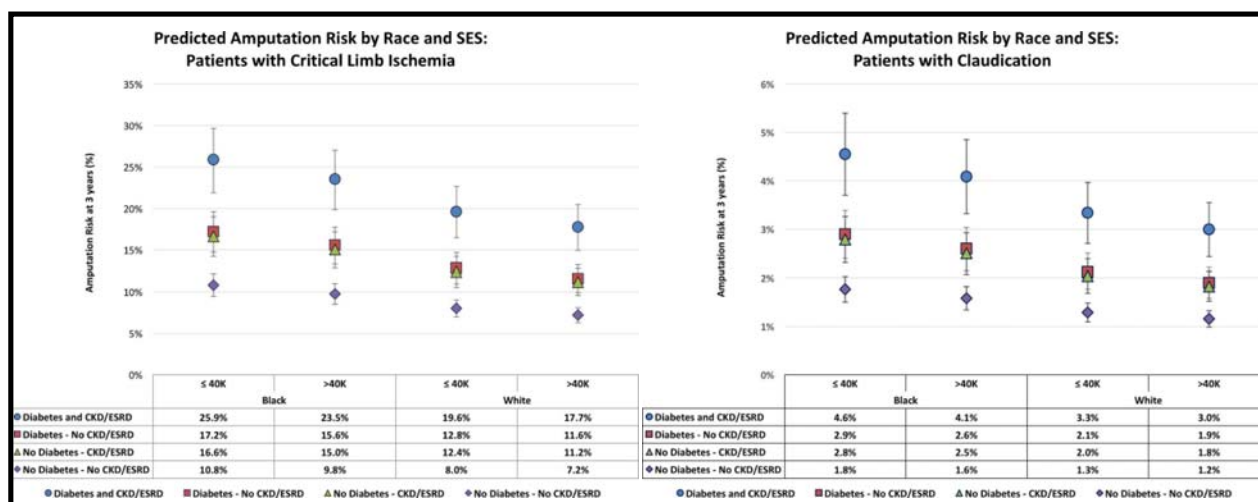
factors, rather than the general adult population as a whole. This could be done by narrowing the recommendation statement to solely focus on the target population, or by creating a second recommendation focused on adults aged 65 and older.

DISPARITIES OF CARE

In addition to our comments above, we would also like to address the draft recommendation statement's potential impact on exacerbating disparities of care. If the recommendation is not revised, we are concerned that it will adversely impact the health care environment for vulnerable populations, including the poor and underrepresented minorities.

The two most significant non-medical attributes that predict poor outcomes in patients with PAD are non-White race and lower socioeconomic status. Jones and colleagues examined the factors associated with amputation in an inpatient Medicare sample from 2000 to 2008.¹² In this population, they report that Black race increases the odds ratio for amputation by 2.9 fold. Similarly, Durazzo and colleagues studied the Nationwide Inpatient Sample from 2002–2008 reporting a 77% excess rate of amputation compared with revascularization for Black patients and a 63% excess for those residing in the poorest 25% of zip codes.¹³ Excess rates of amputation are similarly documented in Hispanic patients.¹⁴ Indeed, both Black and Hispanic patients tended to present much later in the course of PAD, increasing the risk of adverse outcomes.

The question is why that is happening. One important reason is poor access to the medical system.¹⁵ Even in the Medicare population, Tan and colleagues demonstrated that in frail-community dwelling older Black and White subjects, Black subjects were less able to afford supplemental insurance coverage through Medicare or private companies.¹⁶ In this study, despite younger age, Black patients had worse functional status at study enrollment. When access to care was increased, Black patients did as well or better than White patients, showing that care access is key to improvement.¹⁶ These factors become clear in a study using the Healthcare Cost and Utilization Project (HCUP) national inpatient database.¹⁷ Mustapha and colleagues show that both Blacks and Hispanics are approximately twice as likely as Whites to undergo amputation, more likely to show up with advanced disease, and more likely to arrive on an emergent basis. Arya and colleagues bring together all of these factors in a study using the Veterans Affairs Corporate Data Warehouse examining patients with incident PAD from 2003 to 2014.¹⁸ The authors show that Black patients had a higher amputation risk in each socioeconomic stratum compared to white patients (see figure below). This remained true independent of clinical presentation, diabetes, and chronic kidney disease. Moreover, there was no interaction between socioeconomic status (SES) and race. SES independently predicted amputation controlling for race, presentation, diabetes, and chronic kidney disease.



These results strongly suggest that access to care, including preventive care, can reduce healthcare disparities and improve outcomes. The importance of access to care was studied by Loehrer and colleagues.¹⁹ They examined the impact of insurance expansion in Massachusetts. Prior to expansion, there was a 12-13% higher probability for non-White patients to present with critical limb ischemia and gangrene, a decreased likelihood to undergo revascularization, and an increased likelihood to have amputation. Insurance expansion abolished these differences.

Currently, there is no mechanism for PAD discovery in the patient without classic symptoms. The Task Force itself notes that 80-90% of patients are either asymptomatic or atypically symptomatic. The primary care community does not include pulse examination in the routine adult well examination.²⁰ Indeed, in a CME activity in the official American Association of Family Practice journal, when a patient asks about being checked for PAD because a friend of his had a bypass, the answer is to “counsel him that screening him for PAD would have few or no benefits.”²¹ The case study was “based on the recommendations of the USPSTF.” The answer was not “solicit more history or palpate his pulses”. Unfortunately, the USPSTF recommendations for screening for PAD have inculcated a primary care culture where PAD is neither important enough to ask questions about nor perform a physical exam.

CLOSING

In closing, we reiterate our appreciation for the opportunity to provide feedback on the Draft Evidence Review and Recommendation Statement. PAD is a significant public health problem that, as the Task Force notes, affects more than 8 million older Americans, and leads to increased risk for myocardial infarction and stroke, and can lead to gangrene and amputation. Fortunately, that risk can be reduced by well-established cardiovascular risk reduction therapies. That is why proper diagnosis of PAD is essential.

That is also why we encourage the USPSTF to reconsider its draft recommendation statement. The evidence clearly supports screening for PAD and CVD risk using the ABI in individuals aged 65 and older or with other risk factors. We believe that if the Task Force reexamines its evidence review taking our comments above into account, and narrows the patient population to those most at risk, PAD screening with the ABI will receive an "A" grade. Anything less would be a missed opportunity to reduce the risk of cardiovascular events for the millions of Americans with undiscovered and untreated PAD.

If you have any questions, please contact Susan Bishop of the American Heart Association at (202) 785-7908 or susan.k.bishop@heart.org.

Thank you for your consideration of these comments.

Sincerely,

American College of Cardiology
American College of Radiology
American Heart Association
Society for Vascular Medicine
Society of Interventional Radiology

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