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Dear Dr. Cosby:

Thank you for the opportunity to provide expert advice on the "Draft Research Plan on Screening for Peripheral Artery Disease."

As is known to Congress, NHLBI, and many public health advocacy groups, the evidence base now robustly clarifies that peripheral artery disease represents one of the most common, under-diagnosed, morbid, and mortal of all cardiovascular diseases in the United States. It is common in patients with diabetes and, in contrast to PAD in nondiabetic individuals, it is more prevalent and more commonly asymptomatic.[(1)]

As the tools of evidence-based medicine are best applied within a well-crafted public health context, our comments are intended to provide the Task Force with an efficient and accurate approach to this critical cardiovascular public health topic. This response is provided to enhance your approach to the specific elements of the plan that were released on December 15, 2011.

Proposed Analytic Framework

According to the proposed analytic framework, the US Preventive Services Task Force intends to use an unselected sample of asymptomatic adults to evaluate the effectiveness of ABI screening to improve clinical outcomes for individuals with lower extremity atherosclerotic PAD. We note that there is no scientific rationale for USPSTF to consider an analysis that focuses on application of any atherosclerosis diagnostic method to an unselected adult population.

As for nearly all diagnostic approaches for cardiovascular diseases of adults, the research plan should focus only on adults aged 65 years and older. This cohort has been extensively studied, and the accuracy, efficiency, and safety of PAD detection in this population verified in the evidence base. [(2-5)]

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 major impact for Americans who do not have prior evidence of atherosclerosis. Evaluation of a population less than 65 years of age is unlikely to be helpful. [6-10]

The Framingham Heart Study had by 1970 described the high prevalence of lower extremity PAD in this classic epidemiologic population by assessing the prevalence of claudication as a symptomatic marker of PAD prevalence. The Framingham investigators, and all investigations published since then, have noted that the claudication cohort represented a very small fraction of the total population with PAD. This large cohort study of 2,336 men and 2,873 women between the ages of 28 and 62 years, who were initially assessed at standardized examinations every 2 years since 1948, documented the age-dependent prevalence of PAD. Later studies found that the age-specific annual incidence of intermittent claudication for ages 30 to 44 years was 6 per 10,000 men and 3 per 10,000 women. This incidence increased ten-fold, to 61 per 10,000 men, and nearly twenty-fold, to 54 per 10,000 women, among individuals between the ages of 65 and 74 years. [11-12]

In the 1980s, Criqui and colleagues evaluated the prevalence of PAD in epidemiologic evaluation of a free-living asymptomatic population of 613 men and women. The use of objective noninvasive ABI and pulse-wave velocity techniques defined the prevalence of lower extremity PAD to be 2.5% among individuals 60 years and younger, 8.3% among those aged 60 to 69 years, and 18.8% among those 70 years and older [13]. These data, and an extensive evidence base accumulated since then, have also clarified that the largest burden of PAD is present in individuals without recognized limb ischemic symptoms.

In the 1990s, two large prospective epidemiologic assessments have re-demonstrated a high prevalence of PAD in community-derived individuals. Diehm and colleagues evaluated 6,880 unselected patients in 344 primary-care offices with an entry criteria of age greater than 64 years and a life expectancy of > 6 months. In this cohort, 18% of subjects had PAD, and most subjects did not have any recognizable symptoms. [14]

Similarly, Hirsch and colleagues evaluated 6,979 subjects in 350 primary care practices across the United States, performing an ABI in subjects between the ages of 50 and 69 years with a history of smoking or diabetes, or older than 70 years. In this cohort, PAD was detected in 29% of the study population and less than 12% of individuals so detected had classic claudication symptoms. [15]

In the past, the Task Force has developed age-specific recommendations. For example, in 2011, clinical guidelines to screen adults for hearing loss were based on a baseline age of 50 years or older. In 2010, guidelines for reducing falls in older adults were based on an age of greater than 70 years. In 2009, recommendations on the use of folic acid in women were directed at the vulnerable child-bearing age and visual acuity guidelines are also obviously directed at gaining the clinical benefit that accrues when such preventative recommendations are applied to older Americans. The Task Force has also developed

recommendations examining the benefits of breast and prostate cancer screening in selected age-based population cohorts.

PAD is now widely known to represent one of the most important atherosclerotic syndromes. Non-detection and non-treatment permit disease to progress in a large untreated population and thus individuals suffer preventable heart attack, stroke and, to a lesser degree, amputation.

In this context, it is imperative that the Task Force focus its evaluation of the evidence base that demonstrates that PAD is a disease of older Americans. We strongly recommend that the US Preventive Services Task Force limit its examination on the benefits of ABI screening to individuals age 65 and older.

Key Question #1: Does screening for peripheral artery disease (PAD) with an ankle brachial index (ABI) in asymptomatic adults lead to reduced mortality, reduced morbidity from PAD (e.g., onset of symptoms, amputation, impaired ambulation, impaired function), or reduced cardiovascular morbidity (e.g., myocardial infarction, stroke)? [Does the effectiveness of screening for PAD vary by subgroup (i.e., age, sex, race, risk factors)?]

We note that the effort by the Task Force to bundle disparate screening efficacy outcomes into a single question may create methodologic challenges. The current question could best be divided into specific queries. The evidence base that has evaluated improved cardiovascular event reduction benefits is strong. The evidence base that has evaluated potential claudication improvement is less robust. The evidence base for amputation prevention in unselected adult populations is weak. The evidence base for mortality reduction is poor. USPSTF may sustain its methodologic efficacy within the now very large PAD published database by assuring its focus on clinical questions where the most evidence exists with potential to achieve the greatest positive public health impact.

Key Question #2: What is the diagnostic accuracy (e.g., sensitivity, specificity, positive predictive value, negative predictive value) of ABI as a screening test for PAD in asymptomatic adults? [Does the diagnostic accuracy of ABI screening vary by subgroup (i.e., age, sex, race, risk factors)]?

We note that the work of the Task Force may be facilitated, as is true for all evidence-based assessments, by expanding the data source and method and securing access to high quality sources that are not yet available in the indexed citation sources.

The American Heart Association, for example, has completed a multiyear evaluation of the diagnostic accuracy of the ABI via its Scientific Statement process (e.g., “The Measurement and Interpretation of the Ankle-Brachial Index: A Scientific Statement from the American Heart Association”).

This manuscript contains a careful analysis of the evidence derived by careful review of over 210 published references, and that is summarized in 10 tables and figures. This source could be provided upon request. USPSTF should seek evidence from additional

health professional organizations with expertise in this topic and with access to additional information not currently available in the indexed citation sources.

Key Question #3: What are the harms of screening (e.g., overdiagnosis, overtreatment)? Do the harms of screening vary by subgroup (i.e., age, sex, race, risk factors)?

Based upon on our comprehensive review of the medical literature, we note that the published evidence base contains absolutely no evidence to demonstrate that screening for peripheral artery disease causes harm to patients.

We are, however, concerned that the Task Force may, as it appeared to do in 2005, hypothesize about theoretical harms that were not supported by evidence. Specifically, the Task Force wrote that:

> *"[p]otential harms of screening include false-positive results, labeling, and the adverse events associated with an angiographic workup, including contrast-related events, arterial perforations, hematomas, thromboses, and distal embolizations".*

We note that the use of conjecture and speculation is not an evidence-based methodology. Use of speculative harms in such a method would also permit use of speculative benefits. Thus, the Task Force should use the same evidence requirements for the demonstration of harm that it uses for the confirmation of benefit and avoid the use of anecdote and non-literature-based inference.

Key Question #4-B: Does treatment of PAD in asymptomatic adults lead to improved patient outcomes beyond the benefits of treatment in symptomatic adults, or beyond the benefits of treatment in persons with identified conventional risk factors alone (i.e., diabetes, smoking, hypertension, hyperlipidemia)? Does the effectiveness of earlier treatment of PAD vary by subgroup (i.e., age, sex, race, risk factors)?

We would ask that this Key Question be made more specific and more relevant. First, as the USPSTF work frame is that of "prevention," comparison of diagnostic and treatment interventions in asymptomatic patients to those with symptoms is not relevant. The evidence of the diagnostic and treatment efficacy for individuals with symptomatic PAD (e.g., classic claudication or critical limb ischemia) is proven.

We believe that the Task Force is addressing the following key questions:

> (a) Is there a benefit to identifying and treating patients prior to their presentation with leg symptoms?
>
> (b) Is there a benefit to treating patients beyond what atherosclerosis risk factor modification alone would mandate? We note that this second question poses another serious conjectural comparison, as it assumes that clinicians perform such

risk reduction treatment efficiently now, in this population. The published evidence base demonstrates that such risk factor modification does not now occur in asymptomatic individuals with PAD.

For this question, the Task Force would need to determine only if past cardiovascular event reduction trials have included patients with asymptomatic PAD and, if so, was cardiovascular ischemic event reduction achieved?

We note that it is key for the Task Force to distinguish analyses of the benefits of preventing a cardiovascular ischemic event from the potential benefits of preventing new leg symptoms (which has never been a relevant national clinical question, nor the focus of clinical research).

Key Question #5: What are the harms of treatment of screen-detected PAD? Do the harms of early treatment of PAD vary by subgroup (i.e., age, sex, race, risk factors)?

As with Key Question #2, the Task Force should utilize published evidence, and not speculation, within its harm assessment methodology.

First, the Task Force must determine if there is harm to non-detection and non-treatment of PAD by the lack of use of targeted screening. We believe that this is a key methodologic focus, as the clinical impact and health economic burden of non-detection has seemed overt.

For the Task Force, the limited use of a simple, accurate, cost-effective, and safe ABI tool to detect PAD deprives patients (patient-focused care) and clinicians (in order to comply with current evidence-based care guidelines) of a large personal and societal opportunity to begin proven medication and lifestyle-based risk reduction therapies before a first heart attack or stroke occurs.

This particular negative "patient-focused outcome" frame – where a "harm" is achieved when patients are deprived access to a risk-free, extremely low-cost diagnostic method – may be new to US Preventive Services Task Force.

Were the Task Force to consider theoretical harms, we note that PAD is a disease with a latent phase (no recognized leg symptoms) that has proven extremely high short-term rates of non-fatal myocardial infarction, stroke, and death. The theoretical psychological "harm" of non-classification may almost certainly be greater than potential misclassification (though this has not been studied). As well, the potential misclassification harm could be (and is) easily managed by low cost, non-invasive testing, including use of a second ABI test.

The other potential harms of screen-detected PAD (e.g., inappropriate use of medications, lifestyle interventions, diagnostic tests, or invasive procedures) are also theoretical and have no evidence base. While it is true that individuals with symptomatic PAD can be considered candidates for endovascular or surgical leg arterial interventions, screen-detected individuals with PAD (by definition those without symptoms) are never

considered candidates for such procedures. The theoretical harms from inappropriate care delivery (use of contraindicated class III treatments) are managed in the United States by clinical care guidelines and by review of hospital privileges.

Individuals with screen-detected, asymptomatic PAD receive standard treatment for atherosclerosis disease risk reduction (e.g. antiplatelet, statin, ACE inhibitor medications and risk reduction lifestyle interventions). Any harms associated with use of risk reduction interventions exist in this population regardless of whether treatment is triggered by the presence of classic risk factors or by an abnormal ABI.

When medication and lifestyle risk reduction interventions are so used, it is proven that benefits far exceed harms, and are highly cost-effective; a US Preventive Services Task Force review of such treatments for PAD would be unlikely to conclude that atherosclerosis treatments have a distinct "harm>risk" ratio as compared to the robust atherosclerosis reduction evidence base.

Therefore, any consideration of the harms associated with the treatment of screen-detected PAD should only include standard atherosclerosis risk reduction (medication and lifestyle) treatments and need not consider potential "harms" of endovascular or surgical leg arterial interventions that, by definition, are outside of the accepted practice of medicine.

In Summary:
We appreciate the opportunity to comment on the Draft Research Plan. We look forward to working with you to ensure a successful assessment that might provide a major beneficial impact on national public health. If you have any questions, please feel free to contact this inter-societal work group via Mr. Joseph LaMountain, the Vascular Disease Foundation's Washington Representative, at 202.288.5124.

Sincerely,

Robert B. McLafferty, MD
President of the Board
Vascular Disease Foundation

Gordon F. Tomaselli, MD, FAHA
President
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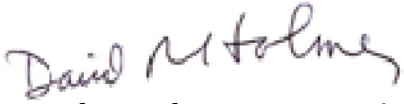

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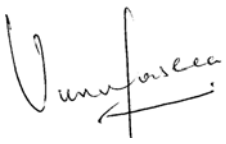

Vivian Fonseca, MD
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