April 20, 2016

USPSTF Coordinator
c/o USPSTF
540 Gaither Road
Rockville, MD 20850

Dear Sir or Madam:

Thank you for the opportunity to comment on the Draft Research Plan for Peripheral Artery Disease in Adults: Screening with the Ankle Brachial Index. We are pleased that the U.S. Preventive Services Task Force (USPSTF) is in the process of updating this recommendation statement.

Peripheral artery disease (PAD) is a common atherosclerotic syndrome that affects approximately 8.5 million Americans and is associated with significant morbidity and mortality. Unfortunately, PAD often goes undiagnosed. Individuals with symptomatic PAD are not informed regarding the significance of these leg symptoms. Thus, they frequently mistake the symptoms, such as cramping, pain or tiredness in the leg or hip muscles upon exertion, for something else. Others – as many as two-thirds of all adults with PAD – are asymptomatic.[1] Left undetected and untreated, PAD increases risk for myocardial infarction and stroke, and can lead to gangrene and amputation.

The ankle brachial index (ABI), however, can easily, painlessly, accurately and inexpensively diagnosis PAD. Since 2005, the American College of Cardiology and the American Heart Association have recommended a single measurement of the ABI to detect patients with PAD, 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 in patients who smoke or have diabetes older than 50 years. This recommendation was reaffirmed in 2011 and again in 2012.[2]

We strongly believe that the evidence base supports the use of the ABI. We hope the Task Force will reach a similar conclusion and recommend ABI screening for older adults and for those with risk factors. However, the current draft research plan is fundamentally flawed. If

[1] Centers for Disease Control and Prevention (CDC). Lower extremity disease among persons aged > or =40 years with and without diabetes: United States, 1999–2002. *MMWR Morb Mortal Wkly Rep*. 2005;54:1158–1160.
[2] In 2005, the ACC/AHA recommendation received a Class I, Level of Evidence C rating. When it was reaffirmed in 2011, the knowledge base on which the recommendation is based had improved, so the recommendation was changed to Class I, Level of Evidence B.

the Task Force proceeds with the proposed research plan, the evidence review will yield a faulty conclusion, as it did in 2013 when the USPSTF last updated this recommendation. Because the draft research plan is, regrettably, very similar to the one used in 2013, we reiterate many of the same concerns in this letter.

Proposed Analytic Framework

According to the proposed analytic framework, the Task Force intends to use an unselected or community-dwelling sample of generally asymptomatic adults to evaluate the effectiveness of ABI screening and determine whether screening leads to improved health outcomes. This frame is not logical and is non-concordant with real world use of the ABI. We remain strongly concerned that the Task Force is focusing on an unselected adult population; there is no scientific rationale to consider an analysis that focuses on application of any atherosclerotic diagnostic method (e.g., ECGs, stress testing, CAC scores, etc.) to an unselected adult population. This frame is a fatal flaw for the proposed analysis.

As for nearly all diagnostic approaches for cardiovascular diseases of adults, the research plan should focus on adults who are at high risk of PAD, including adults aged 65 years and older and those with risk factors. This cohort has been extensively studied, and the accuracy, efficacy, and safety of PAD detection in this population verified in the evidence base.[3,4,5,6]

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. Evaluation of a population less than 65 years of age, or who do not have common risk factors, is unlikely to be helpful.[7,8,9,10,11]

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 population-

[3] Diehm C, Allenberg JR, Pittrow D, et al. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. Circulation. 2009;120:2053– 61.

[4] Fowkes FG. The measurement of atherosclerotic peripheral arterial disease in epidemiological surveys. Int J Epidemiol. 1988;17:248–54.

[5] Feigelson HS, Criqui MH, Fronek A, et al. Screening for peripheral arterial disease: the sensitivity, specificity, and predictive value of noninvasive tests in a defined population. Am J Epidemiol. 1994;140: 526–34.

[6] Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008;300:197–208.

[7] Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA. 2001;286:1317–24.

[8] Diehm C, Schuster A, Allenberg JR, et al. High prevalence of peripheral arterial disease and co-morbidity in 6,880 primary care patients: cross sectional study. Atherosclerosis. 2004;172:95–105.

[9] Resnick HE, Lindsay RS, McDermott MM, et al, Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation. 2004;109(6): 733-739.

[10] Weatherley BD, Nelson JJ, Heiss G, et al. The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study, 1987-2001. BMC Cardiovasc Disord. 2007;7:3.

[11] Newman AB, Siscovick DS, Manolio TA, et al; Cardiovascular Heart Study (CHS) Collaborative Research Group. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Circulation. 1993;88:837-845.

based 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.[12,13]

In the 1980s, Criqui and colleagues evaluated the prevalence of PAD in an 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.[14] 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 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.[15]

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.[16] These data have prospectively demonstrated in real world practice settings that use of easily recognized age and risk factors permit the ABI to serve as one of the single most efficient strategies to detect a very high risk cardiovascular disease.

In the past, the Task Force has developed age-specific recommendations. There are numerous examples, including:

- Screening for impaired visual acuity in older adults (2016) applies to adults aged 65 and older

[12] Kannel WB, Skinner JJ Jr, Schwartz MJ, et al. Intermittent claudication: incidence in the Framingham Study. Circulation 1970;41:875-83.

[13] Hirsch AT, Haskal ZJ, Hertzer NR, et al. American College of Cardiology and American Heart Association 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease. Circulation 2006; 113:e473.

[14] Criqui MH, Fronek A, Barrett-Connor E, et al. The prevalence of peripheral arterial disease in a defined population. Circulation 1985;71:510-5.

[15] Diehm C, Schuster A, Allenberg JR, et al. High prevalence of peripheral arterial disease and co-morbidity in 6,880 primary care patients: cross sectional study. Atherosclerosis. 2004;172:95–105.

[16] Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA. 2001;286:1317–24.

- Screening for breast cancer (2016) offers recommendations based on multiple age groups: 40-49, 50-74, and 75 years and older
- Screening for abnormal blood glucose and type 2 diabetes mellitus (2015) is based on adults aged 40 to 70 years
- Screening for abdominal aortic aneurysm (2014) is based on adults aged 65 to 75
- Screening for dental caries in children (2014) applies to birth through age 5
- Screening for lung cancer (2013) is based on adults aged 55 to 80
- Screening for hearing loss in older adults (2012) applies to asymptomatic adults aged 50 years and older
- Screening for osteoporosis (2011) applies to women aged 65 and older
- Screening for colorectal cancer (2008) offers recommendations based on multiple age groups: 50-75, 76-85, and 85 years and older
- Screening for lipid disorders in adults (2008) offers multiple recommendations for adults aged 20-35 (men), 35 or older (men), 20-45 (women), 45 and older (women), and 20-35 (both men and women)

We believe it would be appropriate 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 strongly recommend that the Task Force limit its examination on the benefits of ABI screening to the population most at-risk for the disease, based on age and risk factors, rather than the general adult population as a whole.

Key Question #1: Is screening for PAD among generally asymptomatic adults with the ABI effective in reducing CVD or PAD morbidity (e.g., impaired ambulation or amputation) or mortality? [Does the effectiveness of screening vary by subpopulation (i.e., age [especially age 65 years and older], sex race/ethnicity, and risk factors?]
We note that the effort by the Task Force to bundle disparate screening efficacy outcomes into a single question will inevitably create methodologic challenges. We are also unaware of any other disease that is associated with morbid outcomes where these two non-biologically-related outcomes – ambulatory symptoms/functional status and cardiovascular events (non-fatal myocardial infarction, stroke, and cardiovascular death) – are combined.

The current question should be divided into specific queries. The evidence base that has evaluated improved cardiovascular risk reclassification is strong. For example, a recent study that compared the Framingham Risk Score alone to an ABI prediction model that incorporates the Framingham Risk Score and the ABI into a single equation found that the ABI model led to improvement in predicting future risk of cardiovascular events.[17]

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 direct-line evidence base for mortality reduction is poor, however the evidence base demonstrating the use of medical therapy is proven to be tightly linked to clinically

[17] Fowkes FGR, Murray GD, et al. Development and validation of an ankle brachial index risk model for the prediction of cardiovascular events. *Eur J Prev Cardiol*. 2014 March; 21(3): 310–320. doi:10.1177/2047487313516564.

meaningful health outcomes (e.g., statin use in asymptomatic atherosclerosis cohorts). Moreover, there is now a Food and Drug Administration-approved medication to be used upon diagnosis of PAD that reduces cardiovascular events and will not be used based on extant risk factors alone.[18] 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 of the ABI as a screening test for PAD among generally asymptomatic adults? [Does the diagnostic accuracy of the ABI vary by subpopulation?]

To answer this question, we recommend that the Task Force examine high quality data sources that have already focused on this question. For example, in 2012, the American Heart Association published 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 Scientific Statement 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. See http://circ.ahajournals.org/content/126/24/2890. We would also suggest that the assessment include studies of the ABI in patients with exertion-related leg pain. All patients with claudication are asymptomatic at rest, when the test is administered, so studies performed in these patients occur in the same condition as patients without leg pain and will expand the evidence base.

Key Question #3: What are the harms of screening for PAD with the ABI? [Do the harms of screening vary by subpopulation?]

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 2013, hypothesize about theoretical harms that were not supported by evidence. Specifically, the Task Force wrote that:

> *The USPSTF found no studies addressing the magnitude of harms of screening for PAD with the ABI; however, the direct harms to the patient of screening itself, beyond the time needed for the test, are probably minimal. Other harms resulting from testing may include false-positive results, exposure to gadolinium or contrast dye if magnetic resonance angiography (MRA) or computed tomography angiography (CTA) is used to confirm diagnosis, anxiety, labeling, and opportunity costs.*

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

[18] Magnani G, Bonaca, MP, et al. Efficacy and safety of vorapraxar as approved for clinical use in the United States. J Am Heart Assoc. 2015 March 19:4(3):e001505. doi: 10.1161/JAHA.114.001505.

harm that it uses for the confirmation of benefit and avoid the use of anecdote and non-literature-based inference.

Consider, for example, the many hundreds of thousands of patients evaluated in prospective NIH and sponsored epidemiologic studies, and in all the current U.S. noninvasive laboratory databases; no harm has been reported. Similarly, manufacturers of ABI diagnostic devices are mandated to report market-detected harms to the FDA. No such harm has been reported. Thus, there is no rationale for speculation about harm.

In addition, because the ABI would be used in lower extremity asymptomatic patients, no further diagnostic testing should be anticipated. Therefore, the USPSTF's concern, according to the Task Force's own procedure manual, about false-positive test results leading to invasive diagnostic protocol for no possible benefit should not apply.

Or, if the USPSTF is concerned about possible psychological harms, we remind the Task Force that the ABI is a blood pressure test. Thus, the same proposed harm applies to a mere arm blood pressure measurement; a screening the Task Force has long recommended for all adults.

Key Question #4: Does treatment of screen-detected or generally asymptomatic adults with PAD or an abnormal ABI lead to improved patient health outcomes? [Does the effectiveness of treatment vary by subpopulation?]

With this question, the Task Force appears to be asking whether there is a benefit to identifying and treating patients prior to their presentation with leg symptoms. We understand why the Task Force has proposed addressing this question, however, we note that the presence or absence of leg pain is a poor indicator for cardiovascular risk. Current epidemiologic data has unambiguously demonstrated the very high rates of myocardial infarction, stroke, and cardiovascular death that occur in individuals with PAD, regardless of leg ischemic symptoms.

The Food and Drug Administration has approved four treatments to reduce cardiovascular events in patients with PAD:

1) Clopidogrel received an FDA label in 1996 and is currently indicated for patients with established PAD.
2) Ramipril is indicated for patients because of a history of peripheral vascular disease based on the HOPE trial.
3) Simvastatin is indicated for patients at high risk for a CHD event due to existing peripheral vessel disease.
4) Vorapaxar is indicated for the reduction of thrombotic cardiovascular events in patients with a history of peripheral arterial disease.

Although the patients in the studies on which FDA-approval was based largely had leg symptoms or a previous lower extremity revascularization, the medications are approved for <u>all</u> PAD patients because cardiovascular risk reduction is not dependent on leg symptoms. The presence of PAD indicates underlying atherosclerosis and a similar final common cardiovascular pathway, no matter the location of its diagnosis. There is <u>no</u> biological or

physiological rationale that can link exertional leg symptoms to the beneficial impact of lipid modifying, anti-thrombotic, or smoking cessation pharmacotherapies or to the proven lowering of short-term cardiovascular risk.

Patients with PAD can benefit from these therapies regardless of whether or not they have leg symptoms. Similarly, exercise trials show that functioning is improved in PAD patients, regardless of whether they have leg pain.

Therefore, we caution the Task Force from suggesting that only patients with leg pain, which is poorly related to the severity of the leg blood flow reduction and related to leg skeletal muscle metabolism, is a reasonable determinant on which to base a therapy for heart and brain blood vessels. We assume the Task Force would not similarly suggest that only patients with diabetes who have symptoms such as excess thirst and urination should be treated.

Key Question #5: What are the harms of treatment of screen-detected or generally asymptomatic adults with PAD or an abnormal ABI? [Do the harms of treatment vary by subpopulation?]

As with Key Question #3, 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. It has been shown that patients who do not receive adequate therapies suffer higher cardiovascular event rates.[19] 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 USPSTF.

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

[19] Pande RL, Perlstein TS, et al. Secondary prevention and mortality in peripheral artery disease: National Health and Nutrition Examination Study, 1999 to 2004. Circulation. 2011 Jul 5:124(1):17-23. doi: 10.1161/CIRCULATIONAHA.110.003954.

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 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.

Contextual Question #1: In primary care, what proportion of patients with an abnormal ABI are generally asymptomatic? [What proportion of generally asymptomatic patients with an abnormal ABI receive additional diagnostic testing? What proportion of generally asymptomatic patients with an abnormal ABI have an ABI of greater than 1.30 or 1.40? What proportion of generally asymptomatic patients with an ABI of greater than 1.30 or 1.40 have PAD?]
We do not have any comments on the appropriateness of the three proposed contextual questions; however, we'd like to take this opportunity to direct the Task Force to research it should consider when answering these questions.

McDermott and colleague screened 1,566 participant in the LIFE study, finding PAD in 14%. Of that group, 65% were asymptomatic.[20] However, the definition of asymptomatic may be inappropriate. In an earlier study of 933 women, among those *without exertional leg pain*,

[20] McDermott MM, Applegate WB, et al. Ankle brachial index values, leg symptoms, and functional performance among community-dwelling older men and women in the lifestyle interventions and independence for elders study. J Am Heart Assoc. 2013 Nov 12:2(6): e000257. doi: 10.1161/JAHA.113.000257.

lower ABI levels were associated with slower walking velocity, poorer standing balance, slower time to arise 5 times, and fewer blocks walked per week.[21]

Based on the ABI collaboration's work, 6-10% of patients have an ABI > 1.3 and 2-3% have an ABI > 1.4. Aboyans and colleagues evaluated the proportion of patients with an elevated ABI with PAD and reported that more than 80% had evidence of PAD by toe brachial index or posterior tibial artery peak flow velocity.[22]

Contextual Question #2: What proportion of generally asymptomatic adults with PAD or an abnormal ABI have lower extremity functional impairment? What is the degree of lower extremity functional impairment, and how does it compare to impairment among patients with reported symptoms (e.g., claudication)?

Grondal and colleagues report a rate of 7.4% of men aged 65 to 74 years have asymptomatic PAD and 3.6% have symptoms in a screening study of 18,749 men.[23] As noted above, McDermott and colleague screened 1,566 participant in the LIFE study, finding PAD in 14%. Of that group, 65% were asymptomatic.[24] However, as noted above, the definition of asymptomatic may be inappropriate. In an earlier study of 933 women, among those *without exertional leg pain*, lower ABI levels were associated with slower walking velocity, poorer standing balance, slower time to arise 5 times, and fewer blocks walked per week.[25]

In primary care medical practices, 30% to 60% of patients with PAD report no exertional leg symptoms and approximately 45% to 50% report exertional leg symptoms that are not consistent with classic intermittent claudication. The prevalence and extent of functional impairment and functional decline in PAD may also be underappreciated. Functional impairment and functional decline are common in PAD, even among those who are asymptomatic. Lower extremity ischemia is also associated with pathophysiologic changes in calf skeletal muscle, including smaller calf muscle area, increased calf muscle fat content, impaired leg strength, and impaired metabolic function. People with severe PAD have poorer peroneal nerve conduction velocity compared with people with mild PAD or no PAD. The degree of ischemia-related pathophysiologic changes in lower extremity muscles and peripheral nerves of people with PAD are associated with the degree of functional impairment.[26]

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[21] McDermott MM, Fried L, et al. Asymptomatic peripheral arterial disease is independently associated with impaired lower extremity functioning: The women's health and aging study. Circulation, 2000 101, 1007-1012. http://dx.doi.org/10.1161/01.CIR.101.9.1007

[22] Aboyans V, Ho E, et al. The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects. J Vasc Surg 2008 48: 1197–1203. doi: 10.1016/j.jvs.2008.06.005

[23] Grøndal N, Søgaard R. and Lindholt JS. Baseline prevalence of abdominal aortic aneurysm, peripheral arterial disease and hypertension in men aged 65–74 years from a population screening study (VIVA trial). Br J Surg, 2015; 102: 902–906. doi: 10.1002/bjs.9825.

[24] McDermott MM. 2013. Ibid.

[25] McDermott MM. 2000. Ibid.

[26] McDermott MM. Lower extremity manifestations of peripheral artery disease: The pathophysiologic and functional implications of leg ischemia. Cir Res. 2015:116:1540-1550.

Contextual Question #3: Do generally asymptomatic adults with PAD or an abnormal ABI have the same risk of global CVD events as symptomatic adults with PAD?
As the Task Force itself said in the 2013 report, "The getABI (German Epidemiological Trial on Ankle Brachial Index) cohort was a large, well-conducted prospective study of unselected persons aged 65 years or older not included in the ABI Collaboration. It included a subgroup comparison of CAD and CVD risk in symptomatic persons (n 593) versus asymptomatic persons (n 836) with ABIs less than 0.9. In this cohort, having a low ABI was associated with an elevated risk for CVD events, with no statistically significant difference between symptomatic and asymptomatic persons. In addition, a secondary analysis of the Heart Outcomes Prevention Evaluation randomized trial of ramipril versus placebo in persons with known CVD found no heterogeneity of outcome effects when comparing asymptomatic participants with decreasing levels of ABI and participants with symptomatic PAD."

Summary
We appreciate the Task Force's decision to reexamine its recommendation on screening for PAD using the ABI. However, as we describe above, we are very concerned that the proposed draft research plan is fundamentally flawed and will once again result in a faulty conclusion. Thus, we urge the Task Force to make the following modifications:

- Adjust the "population" to focus on individuals at high risk of PAD, including those aged 65 and older and adults with risk factors
- Divide the "health outcomes" in key question #1 into two separate queries (ambulatory symptoms/functional status vs. cardiovascular events)
- Use the same evidence requirements for "harms" in key questions #3 and #5 that is used to demonstrate benefits. In the absence of documented harm, speculation cannot be applied.
- Eliminate the link between leg symptoms and cardiovascular risk in key question #4 and throughout the research plan

We are confident that these changes will allow the Task Force to conduct a more thorough and more accurate review of the evidence base, and ultimately recommend screening for older adults and for those with risk factors. 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 with the American Heart Association at 202-785-7908 or susan.k.bishop@heart.org or James Vavricek with the American College of Cardiology at 202-375-6421 or jvavricek@acc.org.

Sincerely.

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