February 12, 2018

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

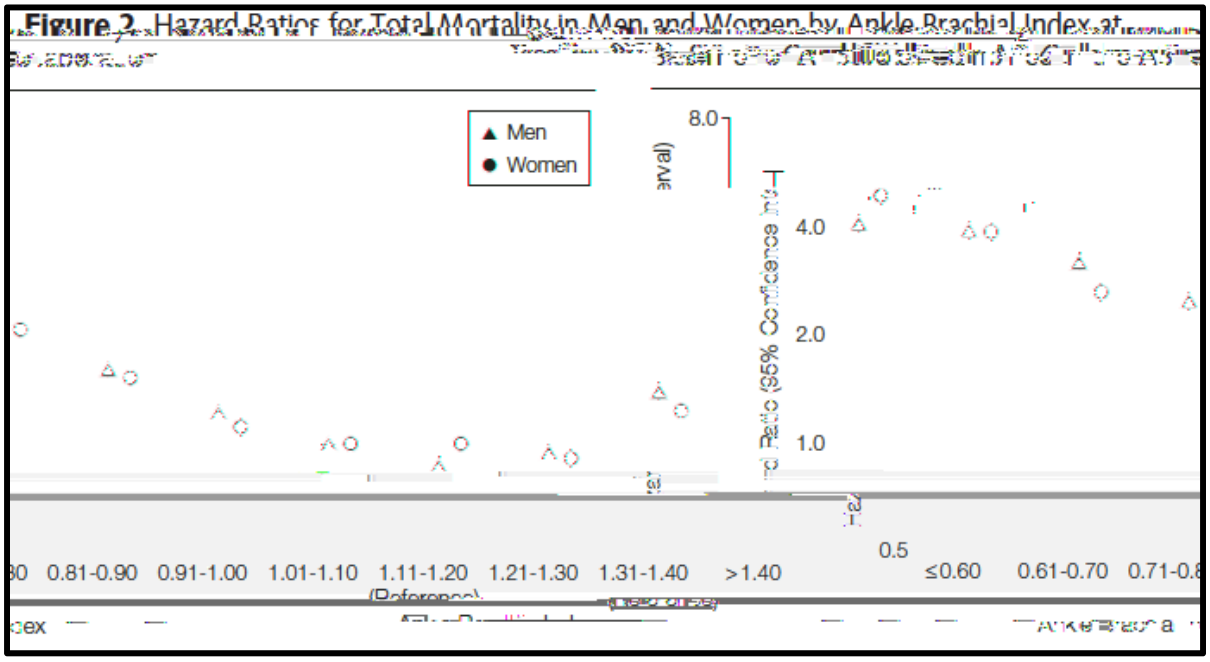
Dear Sir or Madam:

Thank you for the opportunity to comment on the Draft Evidence Review and the Draft Recommendation S♣`

Studies Excluded from the Evidence Review
As part of its review of Key Question 1 (**Is Screening**

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

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

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 patinn ie a / ₹ ṅ/ ¢ / sf ⌈ ʻ ʾ ń E R

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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

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

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]

That is also why we encourage the USPSTF to reconsider its draft recommendation

and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation.* 2009;120:2053-61.
11. Jones WS, Baumgartner I, Hiatt WR, Heizer G, Conte MS, White CJ, Berger JS, Held P,