May 22, 2024

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RE: USPSTF Draft Research Plan on Enhanced Risk Assessment for Cardiovascular Disease: Coronary Artery Calcium Scoring and Ankle Brachial Index

The undersigned organizations appreciate the opportunity to comment on the U.S. Preventive Services Task Force (USPSTF) draft research plan on *Enhanced Risk Assessment for Cardiovascular Disease: Coronary Artery Calcium (CAC) Scoring and Ankle Brachial Index (ABI)*.

Our organizations strongly believe the evidence base supports the use of CAC scoring and ABI. We hope the Task Force will reach a similar conclusion and recommend age-appropriate CAC scoring and ABI measurement for those at risk for atherosclerotic cardiovascular disease (ASCVD), including coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease (PAD).

Coronary Artery Calcium Scoring

CAC scoring is an effective and the most reliable means of risk assessment across patient subgroups for ASCVD events.[1] The 2018 American College of Cardiology (ACC)/American Heart Association (AHA) Multisociety Guideline on the Management of Blood Cholesterol[2] and

[1] Grandhi GR, Mirbolouk M, Dardari ZA, et al. Interplay of coronary artery calcium and risk factors for predicting CVD/CHD mortality: the CAC Consortium. *JACC Cardiovasc Imaging* 2020;13:1175-86.

[2] Grundy, S, Stone, N, Bailey, A. et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019 Jun, 73 (24) e285–e350.

the 2019 ACC/AHA Primary Prevention of Cardiovascular Disease[3] recommend consideration of CAC scoring in patients at borderline or intermediate risk after evaluation using the pooled cohort equation (PCE). CAC scoring has also been shown to provide value in select younger patients 30-49 years and in low-risk patients with a family history of cardiovascular disease (CVD).[4]

Ankle Brachial Index

Despite ongoing efforts, more than 8-10 million Americans are living with PAD unknowingly. Patients with PAD exhibit a higher prevalence of atherosclerosis in their coronary, carotid, and renal arteries compared to individuals without PAD, putting them at risk for heart attacks, strokes, amputations, and death when left untreated. This impact is disproportionately felt by communities of color, those of low socioeconomic status, and in underserved regions, leading to significant disparities in treatment and outcomes.

ABI can easily, painlessly, accurately, and inexpensively diagnose PAD. ACC and AHA, in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation, American Podiatric Medical Association, Association of Black Cardiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine, Society for Vascular Nursing, Society for Vascular Surgery, Society of Interventional Radiology, and Vascular & Endovascular Surgery, recently released a joint practice guideline recommending ABI screening among high-risk patients, including patients 65+ years of age; patients 50+ years of age with atherosclerotic risk factors, chronic kidney disease, or a family history of PAD; adults <50 years of age with diabetes and at least one other atherosclerotic risk factor; and individuals with known atherosclerotic disease in another vascular bed (e.g., coronary, carotid, subclavian, renal, mesenteric artery stenosis, or abdominal aortic aneurysm (AAA).[5]

DRAFT RESEARCH PLAN

Our organizations commend the USPSTF for taking the first step with the draft research plan toward reconsideration of its 2018 assessment, *Cardiovascular Disease: Risk Assessment With Nontraditional Risk Factors*. We firmly believe revision of the USPSTF's 2018 decision to not provide a recommendation (or Grade I due to Insufficient Evidence) is necessary and should align with guideline-supported strategies, including ABI and CAC scoring, which can reduce the risk of adverse cardiovascular events in high-risk populations when they are effectively employed.

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[3] Arnett, D, Blumenthal, R, Albert, M. et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019 Sep, 74 (10) e177–e232.

[4] Adelhoefer S, Uddin SMI, Osei AD, Obisesan OH, Blaha MJ, Dzaye O. Coronary Artery Calcium Scoring: New Insights into Clinical Interpretation-Lessons from the CAC Consortium. Radiol Cardiothorac Imaging. 2020

[5] Gornik HL, Aronow HD, et al. 2024 ACC/AHA/AACVPR/APMA/ABC/SCAI/SVM/SVN/SVS/SIR/VESS guideline for the management of lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024:149;e•••–e•••. doi:10.1161/CIR.0000000000001251

Increases in the prevalence of risk factors for heart disease and stroke, such as high blood pressure and obesity, coincide with recent upward trends in death rates from cardiovascular disease following decades of decline, and disparities persist among major U.S. racial and ethnic groups.[6] The tools for prevention and early detection of cardiovascular disease exist but are under-utilized due to barriers of cost, coverage, awareness and education. The USPSTF plays a critical role in improving access to preventive screenings and tests through its recommendations. It is also important the USPSTF recommendations are effectively communicated to be clearly understood by health care professionals and the American public.

We recognize the key role Evidence-based Practice Centers (EPC) play alongside the USPSTF in the evidence review process. We further understand that for many topics with a previous USPSTF recommendation, the USPSTF may direct either the EPC or the Agency for Healthcare Research and Quality (AHRQ) to conduct a targeted evidence update rather than a full evidence update.[7] Because we do not believe all available evidence was considered when the USPSTF made its recommendation for ABI in 2018, we request the literature review for the ABI recommendation reconsideration not be limited to studies published since the 2018 evidence review. For example, the results of a PAD/abdominal aortic aneurysm screening trial (VIVA) were published in 2017 and showed evidence that PAD screening results in a reduced mortality rate;[8] yet, the study was not considered as part of the previous evidence review because the USPSTF said it couldn't isolate the impact of ABI because the trial also looked at AAA and high blood pressure. We believe the USPSTF erred when it concluded the contribution of ABI was unclear when both PAD morbidity and cardiovascular mortality were reduced in this important trial. To the contrary, the study showed ABI screening reduced in-patient total days for PAD by 19 percent and ischemic heart disease by 11 percent compared to the control group.

To ensure all relevant literature has been considered and evidence presented for USPSTF consideration is accurate, the USPSTF states it incorporates expert and peer review of its background documents.[9] Additional reviewers are identified by the EPC as national experts in the field and investigators of sentinel trials. This is critically important as only one EPC has evaluated the data for vascular disease since 2005. We believe outside subject matter expert reviewers are essential to re-review of ABI and CAC scoring, and we urge the USPSTF to assign the review to a new EPC that can bring fresh perspective to the review of these topics. We note that in the creation of guidelines by our organizations, we routinely change the composition of review panels to avoid the risk of ossification of opinion and assessment. As data changes and the assessment of data changes, new evaluations commonly prompt different points of consensus

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[6] Martin et. al. 2024 Heart disease and stroke statistics: a report of U.S. and global data from the American Heart Association. Circulation. Published online January 24, 2024. doi: 10.1161/CIR.0000000000001209

[7] Current Processes: Refining Evidence-based Recommendation Development. U.S. Preventive Services Task Force. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/current-processes-refining-evidence-based-recommendation-development Accessed May 10, 2024.

[8] J.S. Lindholt, R. Sogaard Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. Lancet, 390 (2017), pp. 2256-2265

[9] Current Processes: Refining Evidence-based Recommendation Development. U.S. Preventive Services Task Force. https:// www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/current-processes-refining-evidence-based-recommendation-development Accessed May 10, 2024.

and conclusions. It is our understanding there are nine EPCs, and we recommend that a different one be chosen for this work.

PROPOSED KEY QUESTIONS (KQ)

We want to acknowledge the significant shift in language and focus between the 2015 *Cardiovascular Disease: Risk Assessment With Nontraditional Risk Factors* final research plan and the proposed 2024 draft research plan. The 2015 research plan key questions placed emphasis on using "nontraditional" risk factors alongside "traditional" risk factors for CVD risk assessment and treatment guidance. Our hope is the absence of this terminology in the 2024 draft research plan is intentional and signals a shift toward a more comprehensive approach to risk assessment, possibly encompassing a broader range of factors beyond the traditional and nontraditional dichotomy.

Additionally, the transition in the question wording from "risk assessment" in the 2015 research plan to "enhanced cardiovascular disease risk assessment" in the 2024 draft seems to indicate a desire, and one shared by our organizations, for deeper exploration of risk assessment methods to include CAC scoring and ABI measurement.

However, we do believe the draft research plan could benefit from a more balanced approach that acknowledges the full spectrum of evidence supporting the utility of CAC scoring and the ABI. The research questions should be framed to capture both the benefits and harms (there is an undue emphasis on risks) and incorporate a wide array of studies into the systematic review. Additionally, the USPSTF should critique any potential biases in question framing that may unduly focus on harms or limitations without equal emphasis on benefits.

We are also concerned the current framework might not fully leverage all longitudinal data and large cohort studies. To avoid ignoring large swathes of relevant data, the framework should explicitly aim to integrate findings from both recent large-scale studies and established research, ensuring that newer models and historical data are considered.

As we have expressed in comments during previous reviews, we are concerned the USPSTF intends to use an unselected adult population to evaluate the effectiveness of CAC and ABI scoring and determine whether they lead to improved health outcomes. There is no scientific rationale to consider an analysis that focuses on application of any atherosclerotic diagnostic method, including CAC scores and ABI, to an unselected adult population. The research plan should focus on adults who are at higher risk of ASCVD, including coronary heart disease, cerebrovascular disease, and PAD.

Feedback on Specific Questions

KQ #1:
What is the effectiveness or comparative effectiveness of enhanced cardiovascular disease risk assessment with coronary artery calcium scoring or the ankle brachial index on cardiovascular health outcomes?

We recommend clarifying what "cardiovascular health outcomes" the USPSTF intends to review. According to the Proposed Research Approach, it will include "CVD events (e.g., myocardial infarction, stroke) and mortality," but it is unclear if MI, stroke, and mortality are the *only* outcomes the Task Force will consider. We are concerned this question could underestimate the utility of CAC scoring and ABI by not specifying the types of cardiovascular outcomes considered. For example, will it include functional measures, such as walking impairment, or hard measures, such as amputation, lower extremity revascularization, or hospitalization for PAD? We believe it should. It should also include the range of CAC scores considered. There is extensive evidence suggesting that CAC scoring can dramatically refine risk stratification, especially in intermediate-risk populations. This question should explicitly address different risk stratification categories (low, intermediate, high) to capture the full utility of CAC.

Several studies have investigated the effectiveness of enhanced cardiovascular disease risk assessment with CAC scoring or ABI on cardiovascular health outcomes. These studies provide evidence supporting the use of both CAC scoring and ABI in enhancing cardiovascular disease risk assessment and improving cardiovascular health outcomes.

We draw your attention to the following studies:

Detrano, R., et al. (2008). Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups. New England Journal of Medicine, 358(13), 1336–1345.

Vliegenthart, R., et al. (2005). The Prognostic Value of the Ankle-Brachial Index in Patients with Claudication. New England Journal of Medicine, 344(6), 395–400.

Jacobs Jr, D. R., et al. (2010). Coronary Artery Calcification and Structural and Functional Measures of Peripheral Arterial Health. Circulation, 121(2), 176–184.

KQ #3:
What are the harms of using coronary artery calcium scoring or the ankle brachial index for enhanced cardiovascular disease risk assessment?

While we understand the need to examine potential harms, we are concerned the focus of harms may disproportionately weigh against the proven benefits of CAC scoring and the ABI, especially if not balanced with an equivalent focus on their preventive benefits, such as the avoidance of unnecessary medication in patients with a low CAC score. It is crucial to ensure the framing of this question does not bias the research against finding a net benefit. Therefore, we recommend the establishment of clear criteria for harm to reduce the risk of subjective recommendations.

In addition, the USPSTF should adhere to the same level of evidence for demonstration of harms that it does for benefit.

KQ #4:
Does treatment guided by CAC Scoring or the ABI lead to improved health outcomes?

This question could benefit from greater specificity about which treatments are considered. According to the proposed research approach, it would include the initiation of aspirin, statins, antihypertensive medications, lifestyle modifications, SGLT-2 inhibitors, GLP-1 agonists, and PCSK9 inhibitors. However, it is unclear if the USPSTF will only examine treatments initiated as the result of a CAC or ABI screening, or if the USPSTF will include large randomized controlled trials that demonstrate the effectiveness of medications that have been approved for these conditions. For example, medications with an FDA-approved indication for use in patients with a low ABI.

It is also vital to specify whether the outcomes are short-term or long-term. The question should also address how treatment outcomes differ when guided by CAC or ABI versus traditional risk assessments (quantitative risk score) alone.

We also recommend investigating the potential improvement in ASCVD risk factor profiles, such as LDL-C and systolic blood pressure, in addition to health outcomes. Doing so could provide a more comprehensive understanding of the benefits of risk assessment tools.

We draw your attention to the following studies:

J.S. Lindholt, R. Sogaard Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. Lancet, 390 (2017), pp. 2256-2265

Lindholt JS, Søgaard R, Rasmussen LM, Mejldal A, Lambrechtsen J, Steffensen FH, Frost L, Egstrup K, Urbonaviciene G, Busk M, Diederichsen ACP. Five-Year Outcomes of the Danish Cardiovascular Screening (DANCAVAS) Trial. N Engl J Med. 2022 Oct 13;387(15):1385-1394. doi: 10.1056/NEJMoa2208681. Epub 2022 Aug 27. PMID: 36027560.

KQ #5:
What are the harms of treatment guided by coronary artery calcium scoring or the ankle brachial index?

While it is important to identify potential harms, this question should be balanced with an assessment of the magnitude of the benefits to provide context. For example, if CAC scoring or the ABI leads to increased use of statins, the potential for over-medication and its side effects should be weighed against the reduction in cardiovascular events. Moreover, harms can be physical, such as side effects from medication initiated due to high CAC scores, or psychological, such as anxiety from high quantitative risk scores (e.g., PCE) without corresponding high-risk subclinical ASCVD. There can also be harms from non-detection and non-treatment. The scope of what constitutes “harm” should be explicitly defined.

In addition, the USPSTF should use published evidence from randomized controlled trials where the proof of benefit and harm are studied appropriately, rather than speculation, within its harm assessment methodology.

Other Suggested Key Questions

We recommend a key question should be added to determine if a CAC score of 0 or a normal ABI can identify individuals at low ASCVD risk compared to multivariate cardiovascular disease risk assessments, as this could help streamline the risk stratification process.

Another key question should explore the comparative effectiveness of CAC scoring measured using formal EKG-gated cardiac CT versus non-EKG-gated chest CT for cardiovascular disease risk assessment. It would also be beneficial to investigate the impact on ASCVD risk factor profiles.

PROPOSED CONTEXTUAL QUESTIONS (CQ)

CQ #5:
What is the comparative performance and agreement between PREVENT (Predicting Risk of cardiovascular disease EVENTs) and PCE (Pooled Cohort Equations)? How do 10-year risk scores compare between the two models? What are the strengths and limitations of each of the models?

We recommend removing question #5. While important, this question does not directly relate to the primary focus of CAC scoring and ABI.

PROPOSED APPROACH TO ASSESSING HEALTH EQUITY AND VARIATION IN EVIDENCE ACROSS POPULATIONS

We appreciate that health equity will be considered throughout the review, which we hope signals the need for a more nuanced understanding of risk assessment and treatment strategies in diverse populations.

It is imperative that the USPSTF's recommendations address and mitigate health disparities. Cardiovascular diseases, including PAD and the increasing rates of associated amputations, disproportionately affect racial and ethnic minorities, individuals of lower socioeconomic status, and those in medically underserved areas. Enhanced risk assessment tools like CAC scoring and ABI have the potential to reduce these disparities by providing earlier and more accurate diagnoses, leading to timely interventions that can prevent adverse outcomes such as amputations. Ensuring that these tools are accessible to all populations, especially those at highest risk, is a critical component of health equity.

We also appreciate that population age is listed as one of the participant characteristics that the USPSTF plans to describe in its evidence review. ASCVD is the leading cause of death in America. The heart and lower extremities are the most commonly impacted by atherosclerotic disease. Numerous independently funded, population-based studies have demonstrated that both coronary and peripheral arterial disease 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 individuals who do not have prior evidence of atherosclerosis. Similarly, PAD is efficiently detected in persons aged 50-64 years in the presence of diabetes and/or a smoking history. Evaluation of a population less than 65 years of

age, or who do not have common risk factors, is unlikely to be helpful.[10,11,12,13,14] Therefore, the USPSTF should limit its examination on the benefits of ABI screening to the population at-risk for the disease, based on age and risk factors, rather than the general adult population as a whole.

CAC scoring and assessment of risk allows for primary prevention, before a cardiovascular event occurs. Further, as 'seeing is believing,' the CAC score test is anticipated to increase adherence by helping patients visualize or understand their risk. In the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study, the addition of CAC score to standard risk factor determinations led to lower waist circumference and Framingham Risk Score (FRS).[15] The USPSTF should limit its examination on the benefits of CAC score screening to the populations with intermediate risk for ASCVD, based on age and risk factors, rather than the general adult population as a whole.[16]

PROPOSED RESEARCH APPROACH

Populations Category

As noted above, we advise examining CAC scoring and the ABI by age, in addition to sex, race, ethnicity, and comorbidities characteristics. We propose removing chronic kidney disease and chronic inflammatory disease from the excluded populations. While chronic kidney disease and chronic inflammatory disease are associated with an increased risk of ASCVD, there are also other diseases with an increased risk of ASCVD that do not exclude patients from CAC scoring.

Interventions Category

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

[11] 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.

[12] 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.

[13] 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.

[14] 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.

[15] Rozanski A, Gransar H, Shaw LJ, Kim J, Miranda-Peats L, Wong ND, et al. Impact of coronary artery calcium scanning on coronary risk factors and downstream testing the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. J Am Coll Cardiol. 2011;57(15):1622–32. Epub 2011/03/29. doi: 10.1016/j.jacc.2011.01.019. PubMed PMID: 21439754

[16] ACC/AHA ASCVD Risk Calculator Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S49–73. Epub 2013/11/14. doi: 10.1161/01.cir.0000437741.48606.98.

Because heart failure is excluded as a "condition definition," we recommend removing SGLT-2 inhibitors, as they primarily reduce the risk of heart failure rather than ASCVD.[17] The USPSTF may also want to consider combining statins and PCSK9 inhibitors into a single category of "lipid lowering medications" since there are other lipid-lowering medications not listed that have also been demonstrated to reduce the risk of ASCVD. We also recommend removing the FRS, as the pooled cohort equation (PCE) and PREVENT (Predicting Risk of CVD EVENTS) equations have replaced the FRS.

Outcomes Category
We suggest examining CVD mortality rather than total mortality to better assess the direct impact of interventions. For *KQs 1, 4, and 5* prospective observational cohort studies would be most appropriate given the focus on cardiovascular risk assessment. Additionally, for *KQ 2*, it remains unclear what data would be used for the prognostic prediction model studies. As per *KQ 1, 4, 5* we recommend using prospective observational cohort studies for *KQ 2*.

CONCLUSION

We appreciate your consideration of our recommendations which we believe will enhance the robustness and relevance of the research plan. We appreciate the opportunity to contribute comments on this draft research plan. Please direct any questions or concerns to Amanda Stirling, ACC Regulatory Affairs Associate, at (202) 375-6553 or astirling@acc.org or Camille Bonta, ABC Policy Advisor, at (202) 320-3658 or cbonta@summithealthconsulting.com.

Sincerely,

Association of Black Cardiologists
American College of Cardiology
American Heart Association
American Society of Nuclear Cardiology
Outpatient Endovascular and Interventional Society
Society for Cardiovascular Angiography & Interventions
Society for Vascular Surgery

[17] Butler J, Jones WS, Udell JA, Anker SD, et al. Empagliflozin after Acute Myocardial Infarction. N Engl J Med. 2024 Apr 25;390(16):1455-1466.