



SOCIETY OF
CARDIOVASCULAR
COMPUTED TOMOGRAPHY

ACRTM
AMERICAN COLLEGE OF
RADIOLOGY



AMERICAN
COLLEGE *of*
CARDIOLOGY

February 12, 2018

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

RE: Draft Evidence Review and Draft Recommendation Statement on Cardiovascular Disease:
Risk Assessment with Nontraditional Risk Factors – Coronary Artery Calcium Scoring

Dear Sir or Madam:

The Society of Cardiovascular Computed Tomography (SCCT), the American College of Cardiology (ACC) and the American College of Radiology (ACR) appreciate the opportunity to submit comments on the USPSTF draft recommendation with respect to coronary artery calcium (CAC) scoring. To date, CAC screening has been studied in more than 100,000 patients, including multiple large prospective studies with up to 15-year follow-up. There are in excess of 1000 peer reviewed publications on CAC from single site observational studies, multicenter cohorts, and randomized trials. Across these studies, CAC has demonstrated a consistent ability to more accurately assess cardiovascular risk in asymptomatic patients beyond that provided by alternative noninvasive tests and risk calculators. It has also been shown that CAC scoring leads to more appropriate use of guidelines-based preventive therapies such as statins and blood pressure lowering therapies.

As such, we believe that the current evidence would support selective offering of this service to individual patients, as there is no significant evidence of any harm with use of CAC, with at least moderate certainty of benefit, when used on selected patients in whom there is uncertainty regarding risk level or the need for preventive therapies, such as statins. Below we to highlight some of our concerns with the current USPSTF draft.

Impact of CAC scoring Compared to the Framingham Risk Score or the Pooled Cohort Equations

There is abundant evidence that global risk scores, such as the Framingham Risk Score (FRS) or Pooled Cohort Equations (PCE), poorly estimate risk across the majority of at risk individuals, including women, younger men, and non-white individuals. Traditional risk scores also underestimate risk in those with a family history of premature ASCVD. CAC has been reported to improve risk assessment – including calibration, discrimination, or reclassification -- above and beyond global risk scores in hundreds of peer-reviewed manuscripts.

Discrimination

To date, the addition of CAC to any baseline model that predicts cardiovascular disease – whether the FRS or the PCE – has been shown to be highly significant, and more robust than the addition of any other risk-factor or biomarker. The USPSTF draft concluded that “Adding CAC score (18 studies) to various risk assessment models resulted in at least a small, and often larger, improvement in discrimination.⁶” However, the review focuses on “The one study²² that added CAC score to the PCE found an improvement of only 0.02 to the area under the curve.” This study does not provide an accurate measure of discrimination because the actual PCE score was not used. Instead, the authors created “a calibrated pooled cohort equation (cPCE), which used the baseline survival estimate from the MESA data..[in order to reduce] the risk overestimation presented in the original PCE/score.”

In fact, when CAC was added to the actual PCE based statin treatment groups identified by the 2013 ACC/AHA guidelines, there was a significant improvement in accuracy of risk assessment, which was driven by appropriate downward reclassification (CAC=0 in 45% of individuals who were recommended statin who had an observed event rate <0.5% per year; CAC=0 in 57% of individuals who were considered for statin therapy who had an observed event rate <0.2% per year).

Reclassification

The incremental value of CAC screening is most evident among patients categorized as intermediate risk by traditional measures. In the MESA and Heinz-Nixdorf Recall (HNR) studies, net reclassification improvement was achieved in 53% and 66% of patients deemed intermediate risk by standard assessment. Importantly, there is no other test (or combination of tests) that has ever been shown to achieve such robust net reclassification improvement, and this net reclassification improvement achieved by CAC is due to both individuals who have events and those with no-events.

The current USPSTF draft states that “CAC score tended to have negative event net reclassification (i.e., more persons who did not have a CVD event were incorrectly reclassified to a higher risk category than were correctly reclassified to a lower risk category)”. This is not

correct and is not supported by data. The vast majority of those with CAC score of zero who are reclassified to a lower risk group, do not have events. And the majority of individuals who do not experience an event have a CAC score of zero and are correctly reclassified to a lower risk category.

The draft states that “Because only a few persons have CVD events (myocardial infarction, stroke, or CVD death) in a given time period compared to the majority of the population, this suggests that on balance, more persons would be inappropriately than appropriately reclassified.⁶” This statement is also incorrect. While it is correct -- for CAC, and for any risk assessment tool -- that most patients reclassified to a higher risk group will not have events, the event rate within this group is still substantially higher.

Utility of CAC scoring when added to the Pooled Cohort Equations

The current draft recommendation states that “studies are needed that measure the effect of adding the ABI, hsCRP, or CAC score to the PCE on clinical decision thresholds and patient outcomes”. We would like to point out that the study by Nasir et al in JACC 2015 provides key data in this regard, and was inappropriately interpreted. This study shows that among those considered (ASCVD score of 5-7.5%) for or recommended (ASCVD score 7.5-20%) statins, approximately 50% of individuals had CAC=0 and subsequently an observed 10-year ASCVD risk of <5%, well below the guideline-based threshold for treatment. Conversely, those with CAC in these groups had an observed 10-year ASCVD risk which was well above the treatment threshold. In fact, the presence of CAC often doubles the risk that would be expected based on traditional risk factors, as has now been observed in several large cohort studies. The results by Nasir et al illustrate the important role that CAC serves in shared decision making among patients who may actually meet guideline based threshold, but in whom there is uncertainty regarding their risk profile or need for statin therapy. Given the consistent over-estimation of the PCE, such uncertainty regarding risk is commonly encountered in clinical practice. In such cases, selective use of CAC may provide a more refined measure of risk. As such, Nasir et al provides robust data for selective use of adding CAC to the PCE, with a substantial effect size (i.e. Number needed to test to identify low risk or high-risk patient of 2).

The current draft states: “Although this analysis underscores the potential of CAC to reclassify individuals across the risk spectrum, the body of evidence reviewed for this report suggests that on a population level, the majority of reclassification is for individuals moved to a higher category of risk (i.e., more persons are inappropriately being reclassified to a higher risk than appropriately being reclassified to a lower risk category).” This sentence is not accurate – and is not consistent with data shown in the current systematic evidence report conducted by the USPSTF. In fact, the reclassification afforded by CAC – which is substantially higher than has been achieved with any other test or biomarker – is driven by both *appropriately* reclassifying individuals to high risk and low risk categories.

Safety of CAC Testing: no evidence of harm

The Task Force states that the “Harms of testing for CAC score include exposure to radiation and incidental findingsthat may lead to further invasive testing and procedures....Psychological harms may result from being reclassified in a higher risk category for CVD events.” With respect to this latter point, the Task Force has pointed out that no studies have found any evidence of psychological harms from use of CAC score assessment. To the contrary, studies have shown that those who are found to have CAC are much more likely to implement beneficial preventive lifestyle interventions.

It is important to understand the radiation dose of CAC is extremely low (~1 mSv), akin to mammography and less than annual exposure from natural sources (~3-4 mSv). There has never been any data that exposure to such a low dose of radiation is associated with any harm. Moreover, for many individuals, the need for CAC testing may only be a one-time test. From a safety perspective, it is also noteworthy that CAC testing requires no patient preparation, avoids IV contrast, and can be performed with one breath hold.

With respect to downstream testing, the Task Force point out that “The Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) study, a RCT of CAC score use in an academic setting, found no statistically significant increase in downstream cardiac testing and procedures.²³” While the Task Force identified that a “retrospective study of Medicare data found that use of CAC score increased downstream cardiac testing and procedures compared to use of hsCRP and lipid screening,²⁸”, this study compared different cohorts of individuals and did not adjust for many important differences in characteristics between individuals who undergo CAC testing versus those who were simply tested with lipid testing or a c-reactive protein. Moreover, this study was performed in a Medicare population cohort with an average age of 72 years of age. This is very different from the population where CAC testing has the highest impact (e.g. age 45-70 years of age in most studies). Accordingly, the Systematic Evidence Report cited by the Task Force appropriately concluded that “the limitations of administrative data and the assembly of control groups limit our confidence as to how much, if any, increase in downstream testing may occur following CAC.” This report did not identify any significant issues related to potential harm of CAC scoring with respect to any of the above potential endpoints.

Clinical Benefits of CAC scoring

There are several randomized trials reporting on the value of CAC as compared to no imaging. From the EISNER trial, use of a CAC scan resulted in a lower FRS at 4-years of follow-up when compared to no scanning (p=0.003) (Rozanski JACC 2011). CAC scanning was associated with a net favorable change in SBP (p=0.02), LDL cholesterol (p=0.04), and waist circumference for

those with increased abdominal girth ($p=0.01$), and tendency to weight loss among overweight subjects ($p=0.07$). Furthermore, this trial showed that compared with no scanning, randomization to CAC scanning was associated with superior coronary artery disease risk factor control without increasing downstream medical testing. Further supporting these results, a recent meta-analysis demonstrated that when compared to those with no CAC, individuals who are found to have CAC are more likely to be initiated on aspirin, statin therapy, and blood pressure lowering therapy, or to have such therapies intensified if they were already prescribed at baseline (Gupta et al, JACC CV Imaging 2017).

The current review by USPSTF includes the St. Francis Heart study (Arad JACC 2005) where 1007 patients with CAC $> 80^{\text{th}}$ percentile were randomized to placebo vs atorvastatin. While this study was not powered for a reduction in events, in the subset of patients with CAC > 400 , there was a 42% RRR and a 6.3% ARR with atorvastatin compared to placebo ($p<0.05$). Furthermore, a post-hoc analysis of this study (Mulders JACC Imaging 2012) demonstrated reduced CV events amongst statin-treated patients with a positive family history compared with the placebo group (HR 0.55, $p = 0.040$). Subsequent data calculated a NNT of 19 with statin therapy to prevent 1 CHD-event over 5-years in intermediate risk patients with a CAC score > 100 (Blaha Lancet 2011).

Conclusion

We request that USPSTF incorporate the above information as part of reconsidering the grade recommendation for CAC scoring. We believe the current data supports selective use of CAC scoring as a complementary, additive risk tool to traditional risk approaches such as the PCE. Importantly, there is abundant data that the PCE over-estimates risk across most patient populations. As such, the most important role of CAC is in shared decision making, when clinicians or patients, or uncertain regarding the role of preventive therapies, such as statins. In such cases, CAC scoring provides superior risk prediction, and leads to better adherence with preventive therapies and lifestyle measures which are known to improve outcomes.

The available data definitively demonstrates that there is a net benefit in using CAC for cardiovascular disease risk assessment. As such, CAC testing should be offered for selected patients in the context of shared decision making, and for the purposes of improving risk assessment, when data from such testing will result in beneficial changes in medical management. Importantly, the 2013 ACC/AHA Guidelines for Assessment of Cardiovascular Risk and Treatment of Cholesterol include CAC scoring as a test that may be appropriate in individuals where treatment decisions for cholesterol or risk assessment is unclear after using the PCE or where additional shared decision making is needed in select individuals.

In summary, the current evidence strongly supports a grade “C” recommendation of selectively offering CAC to individual patients based on professional judgment and patient preferences.

Failing to support such a recommendation would disregard decades of rigorous scientific data in this field, and would deprive countless patients, and their physicians, of the benefit of this test.

We would be delighted to provide any additional information, and may be contacted via the following: Joanne Olson (joloson@scct.org); James Vavricek (jvavricek@acc.org); Anita McGlothlin (amcglathlin@acr.org).

Thank you for your strong consideration of these comments.



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