JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Risk Assessment for Cardiovascular Disease With Nontraditional Risk Factors
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Cardiovascular disease (CVD) is the most common cause of death among adults in the United States. Treatment to prevent CVD events by modifying risk factors is currently informed by the Framingham Risk Score, the Pooled Cohort Equations, or similar CVD risk assessment models. If current CVD risk assessment models could be improved by adding more risk factors, treatment might be better targeted, thereby maximizing the benefits and minimizing the harms.

OBJECTIVE To update the 2009 US Preventive Services Task Force (USPSTF) recommendation on using nontraditional risk factors in coronary heart disease risk assessment.

EVIDENCE REVIEW The USPSTF reviewed the evidence on using nontraditional risk factors in CVD risk assessment, focusing on the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP) level, and coronary artery calcium (CAC) score; the health benefits and harms of CVD risk assessment and treatment guided by nontraditional risk factors combined with the Framingham Risk Score or Pooled Cohort Equations compared with using either risk assessment model alone; and whether adding nontraditional risk factors to existing CVD risk assessment models improves measures of calibration, discrimination, and risk reclassification.

FINDINGS The USPSTF found adequate evidence that adding the ABI, hsCRP level, and CAC score to existing CVD risk assessment models results in small improvements in discrimination and risk reclassification; however, the clinical meaning of these changes is largely unknown. Evidence on adding the ABI, hsCRP level, and CAC score to the Pooled Cohort Equations is limited. The USPSTF found inadequate evidence to assess whether treatment decisions guided by the ABI, hsCRP level, or CAC score, in addition to risk factors in existing CVD risk assessment models, leads to reduced incidence of CVD events or mortality. The USPSTF found adequate evidence to conceptually bound the harms of early detection and interventions as small. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of using the ABI, hsCRP level, or CAC score in risk assessment for CVD in asymptomatic adults to prevent CVD events.

CONCLUSIONS AND RECOMMENDATION The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adding the ABI, hsCRP level, or CAC score to traditional risk assessment for CVD in asymptomatic adults to prevent CVD events. (I statement)

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The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific clinical preventive services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendation and Evidence

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adding the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP) level, or coronary artery calcium (CAC) score to traditional risk assessment for cardiovascular disease (CVD) in asymptomatic adults to prevent CVD events (I statement) (**Figure 1**).

See the Clinical Considerations section for suggestions for practice regarding the I statement.

Rationale

Importance

Cardiovascular disease is the most common cause of death among adults in the United States. Treatment to prevent CVD events by modifying risk factors is currently informed by the Framingham Risk Score, the Pooled Cohort Equations, or similar CVD risk assessment models. If current CVD risk assessment models could be improved by adding more risk factors, treatment might be better targeted, thereby maximizing the benefits and minimizing the harms.

Detection

The USPSTF found adequate evidence that adding the ABI, hsCRP level, or CAC score to existing CVD risk assessment models (Framingham Risk Score [which estimates a person's 10-year risk of coronary heart disease] or Pooled Cohort Equations [which estimate 10-year risk of myocardial infarction, death from coronary heart disease, or stroke]) may improve calibration (agreement between observed and predicted outcomes), discrimination (ability to distinguish between people who will and will not experience an event), and reclassification (ability to correctly reassign people into clinically meaningful risk strata). The USPSTF chose to review these 3 nontraditional risk factors because prior evidence reviews identified them as the most promising to improve on existing CVD risk assessment tools.

Benefits of Risk Assessment and Intervention

The USPSTF found inadequate evidence to assess whether treatment decisions guided by ABI, hsCRP level, or CAC score test re-

sults, when added to existing CVD risk assessment models, lead to reduced incidence of CVD events or mortality.

Harms of Risk Assessment and Intervention

The USPSTF found adequate evidence to bound the harms of risk assessment and intervention as small. When direct evidence is limited, absent, or restricted to select populations or clinical scenarios, the USPSTF may place conceptual upper or lower bounds on the magnitude of benefit or harms. Harms can include abnormal test results, inappropriate risk reclassification, and incidental findings leading to additional testing and possible procedures, as well as anxiety.

USPSTF Assessment

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adding the ABI, hsCRP level, or CAC score to traditional risk assessment for CVD in asymptomatic adults to prevent CVD events.

Clinical Considerations

Patient Population Under Consideration

This recommendation applies to asymptomatic adults without a history of CVD (**Figure 2**).

Suggestions for Practice Regarding the I Statement

Although in the United States both the Framingham Risk Score and the Pooled Cohort Equations are used in practice, the USPSTF recommends that clinicians use the Pooled Cohort Equations to assess CVD risk and to guide treatment decisions until further evidence shows additional benefit of adding other CVD risk factors.

Potential Preventable Burden

Cardiovascular disease comprises diseases of the heart and vascular system, including atherosclerosis, cerebrovascular disease, and peripheral artery disease. It is the most common cause of death among adults in the United States, accounting for 1 in 3 deaths each year.[1] Although CVD remains a significant cause of morbidity and mortality, CVD mortality has been decreasing over time in the United States. Currently, the annual incidence of new cases of myocardial infarction and cerebrovascular accident in the United States is 580 000 and 610 000, respectively.[1]

The incidence of CVD varies by sex. Men, on average, develop CVD about 10 years earlier than women.[2] The burden of CVD increases with age. In 2015, the age-adjusted prevalence of coronary artery disease among US adults aged 45 to 64 years was 6.1%, compared with 16.4% among those aged 65 to 74 years and 23.3% among those 75 years or older.[3] In the same year, 2.7%, 5.6%, and 11.2% of US adults in these age groups, respectively, experienced a stroke. Prevalence also varies by race/ethnicity; in 2015, the prevalence of coronary artery disease was 2 times greater among American Indian/Alaskan Native adults than Asian adults (9.3% vs 3.7%, respectively). Prevalence in Hispanic, African American, and white adults was similar, at 5.1%, 5.4%, and 5.6%, respectively.[3] However, strokes were most common among

African American adults (3.7%), followed by white (2.4%), Hispanic (2.4%), American Indian/Alaska Native (2.2%), and Asian (1.4%) adults.

Potential Harms
Testing for hsCRP level and the ABI is noninvasive, and there is little direct harm from the tests. Harms of testing for CAC score include exposure to radiation and incidental findings on computed tomography of the chest, such as pulmonary nodules, that may lead to further invasive testing and procedures. Abnormal test results may lead to further testing, procedures, and lifelong medication use without proof of benefit but with expense and potential adverse effects for the patient. Psychological harms may result from reclassification into a higher-risk category for CVD events.

Current Practice
Only 1 of the risk assessment models currently used in the United States, the Reynolds Risk Score, incorporates hsCRP level into its risk calculation. A number of guidelines, including those from the American College of Cardiology and the American Heart Association, recommend considering hsCRP level, the ABI, or CAC score to clarify treatment decisions for patients whose risk assessment is borderline or unclear using a traditional risk assessment model.

Figure 1. USPSTF Grades and Levels of Evidence

What the USPSTF Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.

Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as
	   the number, size, or quality of individual studies.
	   inconsistency of findings across individual studies.
	   limited generalizability of findings to routine primary care practice.
	   lack of coherence in the chain of evidence.
	As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.

Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of
	   the limited number or size of studies.
	   important flaws in study design or methods.
	   inconsistency of findings across individual studies.
	   gaps in the chain of evidence.
	   findings not generalizable to routine primary care practice.
	   lack of information on important health outcomes.
	More information may allow estimation of effects on health outcomes.

The USPSTF defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.

USPSTF indicates US Preventive Services Task Force.

Figure 2. Clinical Summary: Risk Assessment for Cardiovascular Disease With Nontraditional Risk Factors

Population	Adults
Recommendation	No recommendation. Grade: I (insufficient evidence)

Risk Assessment	Several traditional risk factors are associated with higher risk for CVD events, including older age, male sex, high blood pressure, current smoking, abnormal cholesterol levels, diabetes, obesity, and physical inactivity. Risk factors can be combined in many ways to classify a person's risk for a CVD event. CVD risk assessment in the United States has been generally based on the Framingham Risk Score and the Pooled Cohort Equations.
Screening Tests	ABI is the ratio of the systolic blood pressure at the ankle (measuring the pressure proximal to the dorsalis pedis or posterior tibial artery) to the systolic blood pressure at the brachial artery. A value <0.9 indicates peripheral artery disease. hsCRP is a serum protein involved in inflammatory and immune responses; the test involves a single blood sample and is widely available. A threshold of >2 or 3 mg/L indicates increased cardiovascular risk. CAC score is obtained by electron-beam or multidetector CT, which measure the calcium content in the coronary arteries. Scoring systems and thresholds for an elevated CAC score vary, but the baseline comparison is often a score of 0.
Treatments and Interventions	Asymptomatic adults at increased risk for CVD are usually treated with a combination of diet and exercise modifications, statins, aspirin, blood pressure management, and smoking cessation interventions.
Other Relevant USPSTF Recommendations	The USPSTF has made recommendations on many factors related to CVD prevention, including screening for high blood pressure, statin use, counseling on smoking cessation, counseling on healthful diet and physical activity, screening for peripheral artery disease and CVD risk assessment with ABI, and low-dose aspirin use in certain persons at increased risk for CVD.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to https://www.uspreventiveservicestaskforce.org.

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ABI indicates ankle-brachial index; CAC, coronary artery calcium; CVD, cardiovascular disease; CT computed tomography; hsCRP, high-sensitivity C-reactive protein; USPSTF, US Preventive Services Task Force.

Assessment of Risk

Accurate identification of persons at high risk for CVD events, particularly nonfatal myocardial infarction or stroke, and CVD death provides the opportunity for more intensive risk factor management to reduce the likelihood of such an event. In addition, identifying persons at low risk may allow for a reduction in interventions with a low benefit to risk ratio for those not likely to benefit.

Several traditional risk factors are associated with higher risk for CVD events, including older age, male sex, high blood pressure, current smoking, abnormal cholesterol levels, diabetes, obesity, and physical inactivity. Risk factors can be combined in many ways to classify a person's risk for a CVD event as low, intermediate, or high. Several calculators and models are available to quantify a person's 10-year CVD event risk. The Framingham Risk Score (which estimates a person's 10-year risk of coronary heart disease) was 1 of the first widely used risk assessment tools. Persons with a 10-year CVD event risk greater than 20% are generally considered at high risk, those with a 10-year risk less than 10% are considered at low risk, and those in the 10% to 20% range are considered at intermediate risk. The Pooled Cohort Equations (which estimate 10-year risk of myocardial infarction, death from coronary heart disease, or stroke) were introduced in 2013 and were developed using more contemporary and diverse cohort data, with the inclusion of race/ethnicity and diabetes. Persons with a 10-year CVD event risk less than 7.5% are considered at low risk, and those with a 10-year risk of 7.5% or greater are considered at high risk.[4] The distribution of estimated

CVD risk in the US population is highly influenced by age and sex. Population estimates of the distribution of 10-year CVD event risk assessed by the Pooled Cohort Equations, which categorize risk using somewhat different thresholds, and using 2001-2010 data from the National Health and Nutrition Examination Survey show that the vast majority of US adults aged 40 to 49 years have an estimated 10-year CVD event risk of 7% or less (93% of women and 81% of men). Among US adults aged 50 to 59 years, 80% of women and 46% of men have an estimated 10-year CVD event risk of 7% or less; 42% of women and 7% of men aged 60 to 69 years have an estimated 10-year CVD event risk of 7% or less.[5]

Screening Tests

Cardiovascular disease risk assessment in the United States has been generally based on the Framingham Risk Score and, more recently, the Pooled Cohort Equations. However, both have been documented to overestimate and underestimate risk in some persons. Therefore, identification of additional tests (for nontraditional risk factors) that could improve risk prediction, including the ABI, hsCRP level, and CAC score, is of interest.

The ABI is the ratio of the systolic blood pressure at the ankle (measuring the pressure proximal to the dorsalis pedis or posterior tibial artery) to the systolic blood pressure at the brachial artery. A value less than 0.9 indicates peripheral artery disease.[6]

High-sensitivity C-reactive protein is a serum protein involved in inflammatory and immune responses. Testing for hsCRP level

involves a single blood sample, and the test is widely available. A threshold of greater than 2 or 3 mg/L is used in clinical practice to signify increased cardiovascular risk.[7-9]

Coronary artery calcium score is obtained by electron-beam or multidetector computed tomography, which measure the calcium content in the coronary arteries. Scoring systems and thresholds for an elevated CAC score vary across studies, but the baseline comparison is often a CAC score of 0.[10]

Treatment and Interventions

Asymptomatic adults at increased risk for CVD are usually treated with a combination of diet and exercise modifications, statins, aspirin, blood pressure management, and smoking cessation interventions.

Additional Approaches to Prevention

The National Heart, Lung, and Blood Institute provides resources on cardiovascular risk assessment, including a link to an online version of the Pooled Cohort Equations.[11] Healthy People 2020 provides a database of evidence-based resources for achieving Healthy People 2020 goals, including interventions to prevent CVD.[12]

Useful Resources

The USPSTF has made recommendations on many factors related to CVD prevention, including screening for high blood pressure,[13] statin use,[14] counseling on smoking cessation,[15] counseling on healthful diet and physical activity,[16] and screening for peripheral artery disease and CVD risk assessment with the ABI.[17] In addition, the USPSTF recommends low-dose aspirin use in certain persons at increased risk for CVD.[18]

Other Considerations

Research Needs and Gaps

A substantial number of studies demonstrate an association between the ABI, hsCRP level, and CAC score and cardiovascular outcomes, so additional association studies are unlikely to add more information. Similarly, studies assessing nontraditional risk factors in isolation are of limited value, given that current treatment recommendations are based on risk assessment with the Framingham Risk Score or Pooled Cohort Equations. Good-quality studies comparing traditional risk assessment with traditional risk assessment plus the ABI, hsCRP level, or CAC scores are needed to measure the effect of adding nontraditional risk factors on clinical decision thresholds and patient outcomes (CVD events and mortality). Studies are especially needed in more diverse populations (women, racial/ethnic minorities, persons of lower socioeconomic status), in whom assessment of nontraditional risk factors may help address the shortcomings of traditional risk models. In addition, well-designed prospective studies reflective of real-world practice are needed to identify the downstream effects of CAC score on additional testing and procedures.

Discussion

Burden of Disease

Cardiovascular disease is the most common cause of death among adults in the United States, accounting for 1 in 3 deaths each year.

Although it remains a major cause of morbidity and mortality, CVD mortality has been decreasing over time in the United States. Currently, the annual incidence of new cases of myocardial infarction and cerebrovascular accident in the United States is 580 000 and 610 000, respectively.[1]

Scope of Review

The USPSTF commissioned a systematic evidence review[7,19] to update its 2009 recommendation on using nontraditional risk factors in assessment of coronary heart disease risk.[20] Unlike the 2009 recommendation, the current recommendation focuses on 3 nontraditional risk factors—the ABI, hsCRP level, and CAC score. The USPSTF chose these risk factors because they have the most promising evidence base, are reliably measured, are independently associated with CVD risk or CVD events, and the prevalence and distribution of abnormal and normal values have been described in the target population. The review focused on the health benefits (reduction in CVD events, CVD mortality, and overall mortality) and harms of CVD risk assessment and treatment guided by nontraditional risk factors combined with the Pooled Cohort Equations or Framingham Risk Score compared with using either risk assessment model alone. The review also evaluated whether the use of nontraditional risk factors, when added to existing CVD risk assessment models, improves measures of calibration, discrimination, and risk reclassification.

At the same time, the USPSTF also commissioned a separate systematic evidence review to update its 2013 recommendation on screening for peripheral artery disease and CVD risk assessment with the ABI.[21]

Accuracy of Screening Tests

The USPSTF reviewed evidence of whether the ABI, hsCRP level, or CAC score improves calibration, discrimination, or risk reclassification when added to CVD risk assessment models using traditional risk factors. Calibration measures the agreement between observed and predicted outcomes, discrimination measures the ability to distinguish between persons who will and will not have an event, and reclassification measures the ability to (correctly) reassign persons into clinically meaningful risk strata. The USPSTF found 10 articles representing 22 cohorts for the ABI, 25 articles representing 49 cohorts for hsCRP level, and 19 articles representing 10 cohorts for CAC score, although few studies reported all 3 measures; most did not use the published versions of the Framingham Risk Score or the Pooled Cohort Equations as the base model.

In general, all cohort studies examining calibration (5 for the ABI, 9 for hsCRP level, and 8 for CAC score) found that adding 1 of these 3 nontraditional risk factors improved calibration, although preferred measures of calibration were rarely reported and only 1 study (of CAC score) used the Pooled Cohort Equations as a base model. The calibration plots available for hsCRP demonstrate that, although adding hsCRP level improved calibration for some groups, it worsened calibration for others.[22,23] An individual patient data meta-analysis of 18 cohorts found that the ABI improved discrimination when added to the Framingham Risk Score, but only for women.[24] A separate analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort (which was not included in the individual patient data meta-analysis) found no improvement from adding the ABI to the Pooled Cohort Equations.[25] Evidence (25 studies) for adding hsCRP was inconsistent, showing at most a small improvement

in discrimination.[7] In the only study that added hsCRP to the Pooled Cohort Equations (MESA), hsCRP level did not improve discrimination.[25] Adding CAC score (18 studies) to various risk assessment models resulted in at least a small, and often larger, improvement in discrimination.[7] However, the magnitude of improvement decreased as the discrimination of the base model improved. Four studies[25-28] that added CAC score to the Pooled Cohort Equations found a very small to small improvement (0.02-0.04) to the area under the curve.

The evidence for risk reclassification was largely similar to the evidence for discrimination. Different studies used different risk strata, but those that used the Framingham Risk Score as the base model generally used less than 10% for low risk, 10% to 20% for intermediate risk, and greater than 20% for high risk, while studies using the Pooled Cohort Equations as the base model used greater than 7.5% for increased risk. In general, studies found that the ABI, hsCRP level, and CAC score tended to have positive event net reclassification (ie, more persons who had a CVD event were correctly reclassified to a higher-risk category than were incorrectly reclassified to a lower-risk category). The ABI (in women) and CAC score tended to have negative nonevent net reclassification (ie, 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). Because only a few persons in the general population have CVD events (myocardial infarction, stroke, or CVD death) in a given period, this suggests that on balance, more persons would be inappropriately than appropriately reclassified.[7]

Effectiveness of Risk Assessment and Treatment

The USPSTF found only 1 study that directly assessed the potential benefit on clinical outcomes of adding 1 of these 3 nontraditional risk factors to traditional risk assessment models.[29] This fair-quality randomized clinical trial (RCT) assigned asymptomatic volunteers (N = 2137) with no history of CVD to CAC scoring plus risk factor assessment counseling vs risk factor assessment counseling alone. At 4 years, there was no difference in CVD outcomes between the 2 groups; however, the study was not adequately powered to detect a difference in patient health outcomes.[29] The USPSTF found no studies that assessed the incremental benefit on health outcomes of adding the ABI or hsCRP level to traditional risk factor assessment. The Viborg Vascular (VIVA) screening trial[30] recently reported interim results; this trial randomized men aged 65 to 74 years to invitation for a triple screening (screening for high blood pressure, abdominal aortic aneurysm, and peripheral artery disease using the ABI) or no screening and found a decrease in mortality with screening; however, it was not possible to determine how much of the decrease was attributable to screening for peripheral artery disease and how much was attributable to screening for abdominal aortic aneurysm and high blood pressure, both of which are already recommended screenings.

The USPSTF found no trials evaluating the additional benefit of adding the ABI, hsCRP level, or CAC score to traditional risk assessment models for guiding decisions about specific interventions to prevent CVD. The USPSTF found a few studies evaluating the use of a nontraditional risk factor as a single intervention to guide decisions about specific preventive medications compared with usual care. Two RCTs (total N = 4626) compared using the ABI to guide decisions to start aspirin therapy vs usual care and found no ben-

efit in CVD outcomes at 7 years of follow-up.[31,32] However, both studies used atypical cutoff points for diagnosing peripheral artery disease, and the results may not be applicable to current practice. One RCT (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin [JUPITER]; N = 17 802) compared hsCRP screening vs usual care to guide high-intensity statin therapy and found benefit at 1.9 years of follow-up in the reduction of CVD events in the hsCRP group.[9] However, because the study only randomized persons with elevated hsCRP levels, it is not known whether patients with lower hsCRP levels would also have benefited from high-intensity statin therapy. Further, many of these patients met criteria for statin therapy based on traditional CVD risk assessment and would already have been candidates for treatment. One study (n = 1005) of using CAC score to guide statin therapy found no benefit at 4 years in the reduction of CVD events.[33]

A systematic review that addressed the effect of screening with CAC score on risk perception, adherence to medication, and behavioral therapies found only 2 studies comparing traditional CVD risk assessment vs CAC score. Neither of these studies found that screening with CAC score was superior to traditional CVD risk assessment for preventive medication use or risk factor management.[5]

Potential Harms of Screening and Treatment

The main potential harm of adding nontraditional risk factors to CVD risk assessment is radiation exposure from CAC score testing, although the dosage (0.4 to 2.1 mSv) is relatively low.[7] More general potential harms are false-positive test results and subsequent invasive diagnostic procedures (such as coronary angiography). Three studies assessing the effect of CAC score on health care utilization found conflicting results. The Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) study, an RCT of CAC score use in an academic setting, found no statistically significant increase in downstream cardiac testing and procedures.[29] In contrast, a retrospective study of Medicare data found that use of CAC score increased downstream cardiac testing and procedures compared with use of hsCRP and lipid screening,[34] while a second smaller observational study found no difference.[35] A systematic review of 7 studies found that the prevalence of incidental findings on computed tomography for CAC score ranged from 8% to 58%. The ultimate outcomes of subsequent diagnostic procedures for these incidental findings, whether positive or negative, are not known.[36] Two studies found no short-term psychological harms from use of CAC score in CVD risk assessment.[37,38]

Treatment with aspirin and statins to prevent CVD events has some potential harms (specifically bleeding and increased incidence of diabetes, respectively), but these harms are generally accepted to be a reasonable trade-off among persons at higher risk of CVD events.[39]

Estimate of Magnitude of Net Benefit

The USPSTF found adequate evidence that adding the ABI, hsCRP level, and CAC score to existing CVD risk assessment models results in small improvements in discrimination and reclassification. However, the clinical meaning of these changes is largely unknown. Evidence on adding the ABI, hsCRP level, and CAC score to the Pooled Cohort Equations is sparse, which makes it difficult to infer the clinical significance of these findings. The USPSTF found inadequate evidence to assess whether treatment decisions guided

by the ABI, hsCRP level, or CAC score, in addition to risk factors in existing CVD risk assessment models, leads to reduced incidence of CVD events or mortality. Few studies were available and were either underpowered or used atypical test thresholds for intervention. The USPSTF found adequate evidence to bound the harms of early detection and interventions as small. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of using the ABI, hsCRP level, or CAC score in risk assessment for CVD in asymptomatic adults to prevent CVD events.

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF website from January 16, 2018, to February 12, 2018. Many comments expressed belief that the evidence for risk assessment with CAC score was strong enough to warrant a separate positive recommendation. Although adding CAC score to traditional risk assessment models improved discrimination and reclassification, the USPSTF found inadequate evidence that this change would translate into improved health outcomes among asymptomatic patients.

Several comments expressed concern that the USPSTF overestimated the harms associated with CAC score testing (radiation exposure, downstream testing). The USPSTF added language to clarify that it determined that the harms associated with the addition of nontraditional risk factors, including CAC score, are small in magnitude.

Several comments noted that the addition of nontraditional risk factors, especially CAC score, is useful for patients whose risk stratification is unclear or for those who fall into intermediate-risk groups. The USPSTF did not find convincing evidence that adding nontraditional risk factors to traditional risk factors improves reclassification in intermediate-risk groups. As clinical practice moves toward a single threshold for treatment, this concern may no longer be relevant in clinical decision making. Some comments also expressed belief that CAC score testing leads to better adherence to preventive therapies (ie, medications and lifestyle changes). The USPSTF carefully reviewed the available evidence and concluded that CAC score testing showed no benefit over traditional CVD risk assessment in preventive medication use or risk factor control. The USPSTF added language to address this point.

Several comments recommended including more information on the differences between the Framingham Risk Score and the Pooled Cohort Equations as well as population distribution of risk. The USPSTF included information in the Clinical Considerations section to clarify these differences and provide more information on risk in the general US population. Last, comments noted that the USPSTF assessment may not be applicable across sex, race/ethnicity, family history, and socioeconomic status. The USPSTF included language indicating the need for more studies in these subpopulations.

Update of Previous USPSTF Recommendation

This recommendation replaces the 2009 USPSTF recommendation.[20] The previous recommendation considered the evidence on the addition of several risk factors to the Framingham Risk Score. The major change in the current recommendation is that the USPSTF evaluated the Pooled Cohort Equations in addition to the Framingham Risk Score and focused on only 3 nontraditional risk factors—the ABI, hsCRP level, and CAC score.

Recommendations of Others

The American Association of Clinical Endocrinologists' 2017 guidelines include hsCRP level, as part of the Reynolds Risk Score, as a possible CVD risk assessment tool and to stratify borderline cases, and also states that CAC score can be useful in refining risk stratification.[40] The American College of Cardiology and American Heart Association encourage using the Pooled Cohort Equations to assess 10-year risk of an initial hard CVD event (defined as stroke, nonfatal myocardial infarction, or CVD death). If risk-based treatment is still uncertain, they recommend using 1 or more of the nontraditional risk factors (including the ABI, hsCRP level, or CAC score) or family history to help clarify treatment decisions.[4] The Canadian Cardiovascular Society encourages use of a modified Framingham Risk Score risk assessment tool in asymptomatic persons to assess 10-year risk of any CVD event. It recommends judicious use of secondary testing among patients for whom the need for statin therapy is unclear.[41] The European Society of Cardiology uses the Systemic Coronary Risk Evaluation (SCORE) risk charts, which do not include the ABI, hsCRP level, or CAC score, to determine 10-year risk of a fatal CVD event.[42] The UK National Institute for Health and Care Excellence uses the QRISK3 risk tool, which does not include the ABI, hsCRP level, or CAC score, to estimate 10-year risk of a CVD event.[43] The Scottish Intercollegiate Guidelines Network (SIGN) uses the ASSIGN risk score to determine the 10-year risk of a CVD event, which does not include the ABI, hsCRP level, or CAC score.[44]

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