Coronary Artery Calcium Scoring

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DESCRIPTION

Computerized axial tomography, also called CT, CT scan, or CAT scan, is an x-ray technique that uses an x-ray-sensing unit which rotates around the body, along with a computer to create cross-sectional images. The images are generated by a computer synthesis of x-ray transmission data obtained for many different directions in a given plane. Electron beam computed tomography (EBCT) and spiral or helical CT scans are types of CT scans that have very high speeds of image acquisition which eliminate the motion artifact of the beating heart, and thus, permit imaging of coronary artery calcium (CAC). Since coronary artery disease (CAD) may remain silent until a major catastrophic event occurs, it has been hypothesized that detection of coronary calcium in asymptomatic individuals could provide additional data on cardiac risk; this could potentially lead to changes in diet, lifestyle, and treatment management (guiding lipid lowering therapy, and decisions on the use of aspirin). It is thought that these changes could potentially reduce the risk of myocardial infarction (MI).

Coronary artery calcium (CAC) scoring has been investigated as a risk factor for coronary artery disease (CAD) and has been used to further evaluate individuals with known coronary artery disease (CAD). The role of CAC as an independent predictor of risk in the assessment, either alone or in combination with conventional risk factors, of both asymptomatic and symptomatic individuals have been studied.

Coronary calcium levels can be expressed in many ways. The most widely used is the Agatston score, which is a weighted summed total of calcified coronary artery area observed on computed tomography (CT). This value can be expressed as an absolute number, commonly ranging from 0 to 400. These values can be translated into age and sex-specific percentile values.

- 0 – no identifiable disease (low risk)
- 1 to 99 – mild disease
- 100 to 399 – moderate disease
- ≥ 400 – severe disease (high risk)

Coronary Artery Calcium (CAC) Scoring in Asymptomatic Individuals

Clinical Context and Test Purpose
The purpose of coronary artery calcium (CAC) scoring using computed tomography (CT) in asymptomatic patients is to assess who may benefit from preventative interventions (guide in lipid-lowering therapy, decisions on the use of aspirin and to assist in discussions regarding therapeutic lifestyle changes and modifications of cardiovascular risk factors) targeted to minimize the risk of atherosclerotic cardiovascular disease (CVD).

Patients
The population of interest is individuals who are asymptomatic with risk of CAD.

Interventions
The intervention of interest is CAC scoring using fast CT imaging, including electron-beam computed tomography (EBCT) and spiral CT. The setting is a primary care or general cardiology practice to assess the risk of CAD.

Comparators
The comparator of interest is CAD risk factor stratification based on standard risk, such as Framingham risk scores (FRS).

Categories of atherosclerotic cardiovascular disease (ASCVD) risk based on calculators have been also standardized in guidelines:

- Low risk – less than 5% 10-year ASCVD risk
- Borderline elevated risk – 5 to 7.4% 10-year ASCVD risk
- Intermediate risk – 7.5 to 19.9% 10-year ASCVD risk
- High risk – 20% or greater 10-year ASCVD risk

Outcomes
The outcomes of interest include survival, test accuracy, test validity, morbid events (e.g., major adverse cardiac events (MACEs), need for invasive coronary angiography (ICA), and revascularization. Additional intermediate or surrogate outcomes of interest are changes in cardiac risk profile indicators such as smoking, hyperlipidemia, or hypertension.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

The Multi-Ethnic Study of Atherosclerosis (MESA) Trial is an ongoing, multi-center, prospective longitudinal study of asymptomatic individuals across four racial/ethnic groups to evaluate the long-term cardiovascular outcomes with a 10-year follow-up of 6772 asymptomatic participants after baseline risk assessment (including CAC measurement). The MESA study was launched in 2000. In 2008 interim results were published (median follow-up 3.9 years) that suggest that the CAC score is a predictor of subsequent clinically significant coronary heart disease (CHD) and may provide predictive information beyond that provided by standard risk factors, (that is, the Framingham Risk Score [FRS]). The authors reported that after adjustment for standard risk factors, a doubling of the CAC score resulted in a 20% increase in the risk of a major coronary event (myocardial infarction/death from CHD) and a 25% increase in the risk of any coronary event. A limitation of this study was variation in CT acquisition and reading methods across the six study centers. The authors also caution against using the absolute calcium scores cited in the study and note that ethnic-specific calibrations of CAC scores are needed to adjust for baseline differences between different ethnic groups. Another limitation of this interim report is the small number of measured clinical events (72 non-fatal MI, 17 fatal coronary events, and 73 events of angina pectoris).

The data, collected thus far, from the MESA Trial have been studied and reported in multiple published studies.

(2018) The Agency for Healthcare Research and Quality (AHRQ) issued a systematic evidence report for the U.S. Preventative Services Task Force (USPSTF) for non-traditional risk factors in cardiovascular disease risk assessment. The review focuses on three of the most promising nontraditional risk factors: ankle-brachial index (ABI), high sensitivity C-reactive protein (hsCRP), and coronary artery calcium (CAC) score.

KQ2. Does Use of Nontraditional Risk Factors in Addition to Traditional Risk Factors to Predict CVD Risk Improve Measures of Calibration, Discrimination, and Risk Reclassification?

CAC has the smallest body of evidence, owing to the smaller sample sizes of included cohorts; no IPD meta-analysis presents results for the incremental predictive value of CAC. Nonetheless, CAC consistently appears to result in at least small, and often larger, improvements in discrimination in studies evaluating hard outcomes in all participants using published coefficients (0.02 to 0.102) and model development studies (0.02 to 0.05). Five studies report improvement in discrimination and reclassification from adding CAC to the PCE or models with PCE variables: three published coefficient studies evaluating just two cohorts and two model development studies. Categorical NRI from model development studies in all participants ranged from 0.14 to 0.319 (continuous NRI ranged from 0.20 to 0.28); evaluation of separate components of the NRI shows that improvements in NRI are consistently driven by event NRIs much larger than nonevent NRIs, which were commonly negative (when reported), and sometimes statistically significant. A limited number of studies report sex-stratified analyses; however, without IPD meta-analyses, it is unclear if there are any consistent sex differences in discrimination or reclassification. The bias-corrected NRI was not consistently reported or calculable. Based on limited data, the bias-corrected NRI is not consistently greater than the NRI for all participants.

Nine studies evaluate more than one nontraditional risk factor and therefore allow for more direct comparison across ABI, hsCRP, and CAC. Overall, CAC appears to be the most promising nontraditional risk factor to add to traditional cardiovascular risk factor assessment. Only two studies using published coefficients evaluated multiple nontraditional risk factors: one evaluated both the PCE and FRS. This study, using the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, found no improvement in discrimination or reclassification for ABI and hsCRP, but the study was limited to lower-risk people because participants taking a statin were excluded from the analyses. However, in this study, CAC did improve both discrimination and reclassification. The other published coefficient analysis using the Heinz Nixdorf Recall cohort evaluated both ABI and CAC added to the FRS and similarly found greater improvement for CAC than ABI. Six model development studies evaluated more than one nontraditional risk factor in addition to the FRS to predict hard CHD or soft CVD events. Five of these six studies included CAC and found statistically significant improvements in discrimination and reclassification; these improvements were greater than effects seen for either ABI and/or hsCRP.

No studies have evaluated the clinical impact of cardiovascular risk assessment with or without nontraditional risk factors on patient health outcomes. Clinical impact studies should be a priority if any of these nontraditional risk factors are implemented on a targeted population level. Largely speaking, the proliferation of cardiovascular risk assessment literature, particularly model development studies without external validation, will not provide the much-needed clinical answers on nontraditional risk factor assessment. However, there are some exceptions. Given that traditional risk tools can overestimate CVD risk, it is crucial to understand the incremental value of promising nontraditional risk factors on calibration, as well as discrimination and reclassification.

More consistent reporting of calibration plots will allow for better understanding of what individuals will benefit from improved calibration and O:E ratios will facilitate comparison of calibration across studies. To understand the true net benefit of reclassification, robust reporting of event and nonevent NRI, and reporting of integrated measures that weight the erroneous misclassification for nonevent proportionally, are important. More studies in diverse populations will aid in understanding whether there are population segments for whom traditional risk factor assessment may underperform to a greater degree and thereby achieve greater benefit from nontraditional risk factor assessment. External validation studies of extended models with nontraditional risk factors are needed. Apart from the ABI Collaboration IPD meta-analysis, none of the extended models has been externally validated.

Given that CAC appears to be the most promising nontraditional risk factor, an IPD meta-analysis for CAC (including longer follow-up of included cohorts) would be informative in furthering understanding of reclassification in subpopulations (e.g., intermediate-risk groups, those for whom traditional risk factor assessment typically underperforms), and vet what impact a CAC score of 0 has on appropriate downward classification of people at intermediate or high risk by traditional risk assessment. Well-designed prospective studies that are reflective of real-world practice are needed to evaluate the downstream effects of CAC on cardiac imaging and revascularization, as well as incidental findings, since these are common. These include studies that aid in determining whether the identification of incidental findings, and/or increased health care utilization, is a net benefit or net harm.

Based on this systematic evidence report it concluded the following: In the absence of true clinical impact studies reporting cardiovascular morbidity and/or mortality, we need to understand the incremental value of risk prediction with nontraditional risk factors, using calibration, discrimination and reclassification. Despite limitations in the reporting of these performance measures as well as limitations in the measures themselves, we can draw some conclusions. There remains scant information on the incremental value of nontraditional risk factors to help with the problem of miscalibration of traditional cardiovascular risk assessment. Evidence from one large IPD meta-analysis suggests that clinicians could use ABI in addition to the FRS to improve upon discrimination and reclassification in populations for whom the FRS model has poor discrimination. While CAC appears to be the most promising nontraditional risk factor to improve discrimination and reclassification, it is based on a smaller body of evidence which lacks IPD meta-analyses. CAC may also result in additional downstream testing/procedures, and it is unclear whether these sequelae represent a net benefit or harm to individuals. One large RCT shows that high-intensity statin therapy in individuals with elevated hsCRP and normal lipid levels can reduce CVD morbidity and mortality, but it is unclear whether these benefits would not also be applicable to individuals with normal hsCRP. The use of hsCRP-guided therapy has not been evaluated against therapy guided by multivariate cardiovascular risk assessment.

(2017) Gepner et al. prospectively evaluated cardiovascular disease (CVD), coronary heart disease (CHD), and stroke or transient ischemic attack (TIA) events to compare the use of coronary artery calcium (CAC) with carotid plaque scores to predict CVD events; the study used data from the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based cohort of individuals without known CVD. After 11.3 years of follow-up among 4955 participants (mean age, 61.6 years), 709 CVD, 498 CHD, and 262 stroke/TIA events had occurred. CAC score significantly reclassified non-CVD events (3%; 95% CI, 2% to 5%) and CHD events (13%; 95% CI, 5% to 18%). Carotid plaque score did not consistently reclassify CVD or CHD events or nonevents.

(2016) Blaha et al. conducted a study using data from MESA to compare the value of various negative risk markers. The authors evaluated the accuracy of change in risk classification by calculating the net reclassification improvement (NRI) for each of the 13 negative risk markers. During a median of 10.3 years of follow-up among a cohort of 6814, 710 cardiovascular disease (CVD) events occurred. Among all negative risk markers, a coronary artery calcium (CAC) score of 0 was the strongest, with an adjusted mean diagnostic likelihood ratio of 0.41 (SD=0.12) for all CHD. NRI for downward reclassification (10-year CVD risk, <7.5%) of CVD events with CAC scores of 0 in participants with a pretest 10-year CVD risk of 7.5% or higher (n=3833 [3227 participants without events and 606 with events]) was 0.14, higher than other negative risk markers included in the study.

(2016) Nakanishi et al. conducted a study among 13,092 consecutive asymptomatic individuals without known coronary artery disease (CAD) (mean age, 58 years) clinically referred for a coronary artery calcium (CAC) scan between 1997 and 2011 at a university medical center; the study examined the predictive value of CAC for 5- and 15-year mortality rates among men and women. CAC showed an incremental prognostic value over traditional risk factors among men at 5 years (area under curve [AUC], 0.702 vs 0.655; p=0.002) as well as at 15 years (AUC, 0.723 vs 0.656; p<0.001). In women, the incremental prognostic value of CAC was not statistically significant at 5 years (AUC, 0.650 vs 0.612; p=0.065) but was statistically significant at 15 years (AUC, 0.690 vs 0.624; p<0.001).

(2015) Won et al. conducted a single-center cross-sectional study among 328 consecutive asymptomatic patients with type 2 diabetes who underwent computed tomographic coronary angiography (CTCA) between 2008 and 2009 in a hospital in South Korea to evaluate the predictive value of the coronary artery calcium (CAC) score for obstructive coronary plaques (OCP) assessed by CTCA. On the basis of a CAC score of 0, 1 to 10, 11 to 100, or greater than 100, OCPs were found in 2%, 5%, 15%, and 36% of patients, respectively. On receiver operating characteristic curve analysis, the optimal cutoff CAC score for predicting OCPs was found to be 33, with 83% sensitivity and 81% specificity (AUC=0.853; 95% CI, 0.777 to 0.930; p<0.001). Positive and negative predictive values of a CAC score of 33 for OCPs were 30% and 98%, respectively. On multivariate logistic regression analysis, age (odds ratio [OR], 1.09), microalbuminuria levels (OR=3.43),

current smoker (OR= 3.93), and a CAC score greater than 33 (OR=15.85) were found to be independently associated with an increased risk for OCPs ($p<0.05$).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if individuals receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for individuals managed with and without the test. The preferred evidence would be from randomized controlled trials (RCTS).

Observational Studies
(2019) Aljaroudi et al. completed a retrospective study by, reported on 173 participants who had stress echocardiography with concomitant computed tomography coronary angiography (CTCA) to assess the added value of both techniques in comparison with CTCA to exclude CAD. The CTCA exams were performed following stress echocardiography, on the same day. Calcium scoring results and CTCA were read by one cardiologist who was blind to the results of the stress echocardiography. Normal CTCA was noted in 69 participants, non-obstructive CTCA was noted in 83 participants (77 of which had a CAC score > 0, median score 40), and obstructive CTCA was found in 21 participants (all with CAC score > 0, median score 238). Inducible ischemia was found on stress echocardiography in 16 participants (3 had normal CTCA, 3 had non-obstructive CTCA, and 10 had obstructive CTCA results). Normal stress echocardiography had an NPV of 93% to exclude obstructive CAD with NPV of 42% NPV to exclude any CAD (non-obstructive and obstructive). There were 72 participants without ischemia and CAC score of zero (66 had normal CTCA, 6 had non-obstructive CAD, and none had obstructive CAD). There was a 100% NPV for obstructive CAD for a combined normal stress echocardiography and CT calcium scoring and a 92% NPV for any CAD (nonobstructive or obstructive). The authors repeated the same analysis in a validation cohort of 111 participants. In the validation cohort there were 53 participants without ischemia and CAC score of zero (49 with normal CTCA, 4 with nonobstructive CAD and none with obstructive CAD). The combined normal stress echocardiography and CT calcium scoring had an NPV of 100% for obstructive CAD and 92% for any CAD. The study has limitations including lack of family history data, the participant population was from an executive screening program with a low-intermediate risk of major adverse cardiovascular events, and the majority of participants were men (n=114) which does not allow for generalization to the whole population.

(2015) Chang et al. prospectively evaluated whether coronary artery calcium (CAC) scoring added incremental predictive value to exercise treadmill testing and stress myocardial perfusion single-photon emission computed tomography testing when used to assess risk of cardiac events (a composite of cardiac death, nonfatal myocardial

infarction, and the need for coronary revascularization) in a cohort of 988 asymptomatic and symptomatic low-risk patients without known coronary heart disease (CHD). Over a median follow-up of 6.9 years, the cardiac event rate was 11.2% (1.6% per year). Annual event rates were higher in patients with CAC scores above 400 (3.7% per year) compared with those with CAC scores of 10 or less (0.6% per year; $p<0.001$). The addition of CAC score to risk stratification based on the FRS improved risk prediction.

(2015) Johnson et al. assessed the association between coronary artery calcium (CAC) score and subsequent health behavior change. The study included a convenience sample of 174 adults with CHD risk factors who underwent CAC scoring. The authors found no significant between-group change in risk perception measured by Perception of Risk of Heart Disease Scale scores (CAC score range, 0, 1-10, 11-100, 101-400, >400), with the exception of a small increase in the moderate-risk group (CAC score, 101-400) from 55.5 to 58.7 ($p=0.004$). All groups demonstrated increases in health-promoting behavior over time.

(2013) Budoff et al. evaluated the association between coronary calcium scores and coronary heart disease (CHD) events during 5-year follow-up of 2232 adults from MESA (discussed above), and 3119 subjects from the Heinz Nixdorf RECALL (Risk factors, Evaluation of Coronary Calcium and Lifestyle Factors) study. Increasing Agatston scores were associated with increased risk of CHD. In MESA, compared with a CAC score of 0, having a score greater than 400 was associated with a hazard for CHD of 3.31 (95% CI, 1.12 to 9.8) after adjusting for CHD risk factors; a score ranging from 100 to 399 was associated with a hazard of 3.27 (95% CI, 1.19 to 8.95). In the RECALL study, compared with a CAC score of 0, having a score greater than 400 was associated with a hazard for CHD of 2.96 (95% CI, 1.22 to 7.19). Lower CAC scores were not significantly associated with CHD after adjusting for other risk factors.

Randomized Controlled Trials (RCTs)

(2011) Rozanski et al. conducted an RCT to evaluate the impact of computed tomography (CT) scanning for coronary artery calcium (CAC) on cardiac risk factors. A total of 2137 healthy volunteers were randomized in a 2:1 ratio to CT scanning (n=1424) or no CT scanning (n=713) and followed for 4 years. At baseline, both groups received 1 session of risk factor counseling by a nurse practitioner. The primary end point was 4-year change in cardiovascular disease (CAD) risk factors and Framingham Risk Score (FRS). At the 4-year follow-up, there was differential dropout among the groups, with 88.2% (1256/1424) of follow-up in the scan group versus 81.9% (584/713) in the no-scan group. Compared with the no-scan group, the scan group showed a net favorable change in systolic blood pressure ($p=0.02$), low-density lipoprotein cholesterol ($p=0.04$), and waist circumference for those with increased abdominal girth ($p=0.01$), and a tendency to weight loss among overweight subjects ($p=0.07$). While there was a mean rise in FRS in the no-scan group (0.7, SD=5.1), FRS remained static in the scan group (0.002, SD=4.9; $p=0.003$). Downstream medical testing and costs in the scan group were comparable with those of the no-scan group, balanced by lower and higher resource utilization for subjects

with normal CAC scans and CAC scores of 400 or higher, respectively. This trial highlights the potential benefit of CAC screening in modifying cardiac risk profile but is not definitive in demonstrating improved outcomes. Trial limitations included differing intensities of interventions between groups and differential dropout. It is possible that the small differences reported in the trial result from bias related to these methodologic limitations. Also, this trial did not compare the impact of other types of risk factor intervention, most notably more intensive risk factor counseling. Finally, the generalizability of the findings is uncertain because this was a volunteer population that might have been highly motivated for change.

Systematic Reviews

(2022) Bell et al. studied coronary artery calcium scores (CACS) are used to help assess patients' cardiovascular status and risk. However, their best use in risk assessment beyond traditional cardiovascular factors in primary prevention is uncertain. Objective was to find, assess, and synthesize all cohort studies that assessed the incremental gain from the addition of a CACS to a standard cardiovascular disease (CVD) risk calculator (or CVD risk factors for a standard calculator), that is, comparing CVD risk score plus CACS with CVD risk score alone.

The evidence review included eligible studies which needed to be cohort studies in primary prevention populations that used 1 of the CVD risk calculators recommended by national guidelines (Framingham Risk Score, QRISK, pooled cohort equation, NZ PREDICT, NORRISK, or SCORE) and assessed and reported incremental discrimination with CACS for estimating the risk of a future cardiovascular event. The findings were from 2772 records screened, 6 eligible cohort studies were identified (with 1043 CVD events in 17 961 unique participants) from the US (n = 3), the Netherlands (n = 1), Germany (n = 1), and South Korea (n = 1). Studies varied in size from 470 to 5185 participants (range of mean [SD] ages, 50 [10] to 75.1 [7.3] years; 38.4%-59.4% were women). The C statistic for the CVD risk models without CACS ranged from 0.693 (95% CI, 0.661-0.726) to 0.80. The pooled gain in C statistic from adding CACS was 0.036 (95% CI, 0.020-0.052). Among participants classified as being at low risk by the risk score and reclassified as at intermediate or high risk by CACS, 85.5% (65 of 76) to 96.4% (349 of 362) did not have a CVD event during follow-up (range, 5.1-10.0 years). Among participants classified as being at high risk by the risk score and reclassified as being at low risk by CACS, 91.4% (202 of 221) to 99.2% (502 of 506) did not have a CVD event during follow-up. The authors concluded this systematic review and meta-analysis found that the CACS appears to add some further discrimination to the traditional CVD risk assessment equations used in these studies, which appears to be relatively consistent across studies. However, the modest gain may often be outweighed by costs, rates of incidental findings, and radiation risks. Although the CACS may have a role for refining risk assessment in selected patients, which patients would benefit remains unclear. At present, no evidence suggests that adding CACS to traditional risk scores provides clinical benefit.

(2014) Mamudu et al. conducted a systematic review of studies evaluating the effects of coronary artery calcium (CAC) screening on behavioral modification, risk perception, and medication adherence in asymptomatic adults. Fifteen studies were selected (3 RCTs, 12 observational studies). The size of the study populations ranged from 56 to 6814 individuals. Reviewers primarily provided descriptive results of the studies given the lack of standardization across studies regarding CAC measures and outcome variables. CAC screening improved medication adherence. However, the impact of CAC screening on behavioral and lifestyle factors (BMI, diet, exercise, smoking), perception of CAD risk, and psychosocial effects was nonsignificant compared with baseline.

(2013) Xie et al. conducted a systematic review to evaluate the prognostic performance of the coronary artery calcium (CAC) score derived from non-triggered CT. In 5 studies, 34,028 cardiac asymptomatic patients were followed for a mean of 45 months (range, 0-72 months). No meta-analysis was performed on the studies because of large heterogeneity in calcium quantification methods, calcium score categorization, and outcomes. During follow-up, 207 cardiovascular deaths and 675 cardiovascular events were observed. Overall, increasing unadjusted and adjusted hazard ratios (HR) were observed with increasing calcium score categories.

(2012) Whelton et al. published a meta-analysis of randomized controlled trials (RCTs) that evaluated the impact of coronary artery calcium (CAC) scores on cardiac risk profiles and cardiac procedures. Four trials were identified (total N=2490 participants); the individual trials ranged in size from 50 to 1934 patients. Reviewers pooled data from 4 trials on the impact of calcium scores on blood pressure, three to evaluate the impact on low-density lipoprotein, and from two to determine the impact on high-density lipoprotein. Pooled analysis did not show a significant change in any of these parameters when incorporating calcium scores. Similarly, in 4 studies that looked at the rates of smoking cessation following calcium scores, no significant change was found. Two studies included rates of coronary angiography and two included rates of revascularization. Pooled analysis of these studies did not show a significant change after measurement of coronary calcium.

Coronary Artery Calcium (CAC) Scoring in Symptomatic Individuals

In certain clinical situations, such as individuals presenting with chest pain, it is uncertain whether the symptoms are due to CAD. Coronary calcium measurement has been proposed as a stand-alone test to rule out CAD in individuals with symptoms suggestive of myocardial ischemia.

Clinical Context and Test Purpose

The use of coronary artery calcium (CAC) scoring with computed tomography (CT) in symptomatic individuals suggestive of myocardial ischemia can rule out the atherosclerotic etiology of CAD.

Patients
The population of interest includes individuals who have signs and/or symptoms suggestive of myocardial ischemia and predicting significant CAD.

Interventions
The intervention of interest is CAC scoring using fast CT imaging, including EBCT and spiral CT. CAC scoring using CT is administered in a cardiology practice or emergent care setting for individuals undergoing evaluation of chest pain. CT CAC scoring is utilized when individuals require evaluation for persistent stable angina or experience onset of acute chest pain.

Comparators
The comparators of interest standard diagnostic testing which includes functional testing and exercise electrocardiography [ECG].

Outcomes
The outcomes of interest include over survival (OS), test accuracy, test validity, morbid events (e.g., major adverse cardiac events [MACEs], need for ICA (interventional coronary angiography) and revascularization).

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Observational Studies
(2016) Parma et al. assessed the predictive value of CAC in symptomatic individuals, with an intermediate probability of CAD, for the incidence of major adverse coronary events. The single-center, observational, prospective study included 588 symptomatic participants with no previous diagnosis of CAD. Major adverse coronary events included cardiac death, nonfatal MI, and coronary revascularization. There were no coronary calcifications found in 239 of the participants. A total of 349 participants were found to have CAC. Of the participants with CAC, they were also noted to have hypertension, diabetes, hypercholesterolemia, and a positive history of premature CAD. For the participants who had positive results of CAC, the score ranged from 1 to 99 Agatston units (AU) in 172 participants, 100 to 399 AU in 105 participants, 400 to 999 in 38 participants, and greater than or equal to 1000 AU in 34 participants. The median follow-up period was 707 days. During this time, major adverse coronary events occurred in 108 participants (119 events) including 1 cardiac death, 13 nonfatal MI, 72 angioplasties, and 33 bypass surgeries. While this study shows the presence of CAC is a predictor of major adverse coronary events, any previous noninvasive tests were not taken into consideration, and coronary revascularization procedures might have been influenced by the CAC findings.

(2015) Chaikriangkrai et al. retrospectively evaluated whether coronary artery calcium (CAC) added incremental value to computed tomography angiography (CTA) for predicting coronary artery stenosis in 805 symptomatic patients without known coronary heart disease (CHD). CAC score was significantly associated with the presence of coronary artery stenosis on CTA. Both CAC score and the presence of CTA stenosis were significantly associated with MACE (major adverse cardiac event) rates, including cardiac death, nonfatal myocardial infarction, and late coronary revascularization. Patients with more than 50% stenosis on CTA had higher MACE rates, compared with those who had a normal CTA (4.5% vs 0.1%, $p<0.001$) and with those who had less than 50% stenosis (4.5% vs 1.4%, $p=0.002$). Those with a CAC score of more than 400 had higher MACE rates than those with scores between 1 and 100 (4.2% vs 1.4%, $p=0.014$) and those with scores of 0 (4.2% vs 0% $p<0.001$). The addition of CAC score to a risk prediction model for MACE, which included clinical risk factors and CTA stenosis, significantly improved the model's predictive performance (global X2 score, 108 vs 70, $p=0.019$).

(2015) Pursnani et al. published results from a subgroup analysis of the ROMICAT II trial. It evaluated the incremental diagnostic value of coronary artery calcium (CAC) scoring plus computed tomography angiography (CTA) in low- to intermediate-risk patients presenting to the emergency department with symptoms (chest pain or angina equivalent of ≥5 minutes duration within 24 hours) suggesting acute coronary syndrome (ACS). The ROMICAT II trial randomized patients with possible ACS to CTA as part of an initial evaluation or to the standard emergency department evaluation strategy, as directed by local caregivers. As part of the trial protocol, all patients undergoing CTA had a CAC scan; the present analysis included 473 patients who underwent both CTA and CAC scanning. Among these patients, the ACS rate (defined as unstable angina and myocardial infarction during the index hospitalization) was 8% (n=38). Patients with lower CAC scores were less likely to have a discharge diagnosis of ACS. Among 253 patients with a CAC score of 0, 2 (0.8%) patients were diagnosed with ACS (95% CI, 0.1% to 2.8%). Receiver operating characteristic curve analysis was used to predict the risk of ACS by CAC score greater than 0, continuous CAC score, CTA results, and combined CAC and CTA score. The optimal cut point of CAC for ACS detection was 22 (C statistic, 0.81), with 318 (67%) patients having a CAC score less than 22. All CTA strategies had high sensitivity for ACS detection, without significant differences in stenosis thresholds. CAC was inferior to CTA for predicting ACS (C range, 0.86 vs 0.92; $p=0.03$). The addition of CAC score to CTA (i.e., using selective CTA only for patients with CAC score >22 or >0) did not significantly improve the detection of ACS (CAC+CTA C=0.93 vs CTA C=0.92; $p=0.88$). Overall, this trial suggested that CAC scoring does not provide incremental value beyond CTA in predicting the likelihood of ACS in a low- to intermediate-risk population presenting to the emergency department.

(2014) Hulten et al. published results from a retrospective cohort study among symptomatic patients without a history of coronary artery disease (CAD) to evaluate the accuracy of coronary artery calcium (CAC) scoring for excluding coronary stenosis,

using computed tomography angiography (CTA) as the criterion standard. The study included 1145 patients who had symptoms possibly consistent with CAD who underwent non-contrast CAC scoring and contrast-enhanced CTA from 2004 to 2011. For detection of greater than 50% stenosis, CAC had a sensitivity, specificity, and negative predictive value of 98%, 55%, and 99%, respectively. For prediction of cardiovascular death or myocardial infarction, the addition of either or both CAC and CTA to a clinical prediction score did not significantly improve prognostic value.

Randomized Controlled Trials (RCTs)

(2016) Lubbers et al. conducted a multicenter RCT to compare the effectiveness and safety of a cardiac CT algorithm with functional testing in patients with symptoms (stable chest pain or angina equivalent symptoms) suggestive of coronary artery disease (CAD). A total of 350 patients with stable angina were prospectively randomized 2:1 to cardiac CT and functional testing, such as exercise ECG, myocardial perfusion imaging, or stress echocardiography. Patients in the cardiac CT arm (n=242) initially underwent calcium scanning followed by computed tomography angiography (CCTA) if the Agatston calcium score was between 1 and 400. CAD was ruled out if the patients had a CAC score of 0. The original primary end point of the trial was the proportion of patients undergoing catheter angiography followed by revascularization, but because of insufficient funding, authors could not assess that end point and chose clinical effectiveness as the alternative primary outcome, defined as the absence of chest pain complaints after 1 year. After 1-year, fewer patients randomized to CT reported angina symptoms that those in the functional testing group (39% vs 25%, p=0.012), although the proportion of patients with similar or worsened symptoms was comparable (26% vs 29%, p=0.595). The tiered protocol study design is a strength of this study, but the unplanned change in end points limits analysis and conclusions.

Systematic Reviews

(2016) Chaikriangkrai et al. conducted a systematic review and meta-analysis to examine the prognostic value and accuracy of a coronary artery calcium (CAC) score of 0 for identifying patients presenting with acute chest pain at acceptable low risk for future cardiovascular events. The systematic review included only prospective cohort studies that used multidetector computed tomography (MDCT) or electron beam computed tomography (EBCT) to calculate CAC scores using the Agatston method and reported major adverse cardiac events (MACEs) at 1 month and beyond the index emergency department visit. Eight studies evaluating 3556 patients with a median follow-up of 10.5 months were selected. Reviewers conducted a subgroup analysis of 6 studies at predominantly white patients (n=2432 patients) to estimate the prognostic accuracy indices of CAC scores (0, >0) for cardiovascular events (MACEs, all-cause deaths, nonfatal myocardial infarction). Pooled sensitivity, specificity, as well as positive and negative likelihood ratios were 96% (I2=0%), 60% (I2=15.1%), 2.36 (I2=0%), and 0.07 (I2=0%), respectively.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would from randomized controlled trials (RCTs).

Systematic Reviews
The 2016 systematic review by Chaikriangkrai et. al. (discussed above) assessed studies of relevance to our analysis of clinical utility. Specifically, in 8 studies (total N=3556 patients), those with a coronary artery calcium (CAC) score of 0 had a significantly lower risk of MACEs (major adverse cardiac events) compared with patients with CAC scores greater than 0 (RR=0.06; 95% CI, 0.04 to 0.11; $p<0.001$; $I2=0\%$). The risk difference was 0.19 (95% CI, 0.11 to 0.27).

Observational Studies
(2014) Yerramasu et al. prospectively assessed an evaluation algorithm including coronary artery calcium (CAC) scoring for patients presenting to a rapid access chest pain clinic with stable chest pain possibly consistent with coronary heart disease (CHD). Three hundred patients presenting with acute chest pain to 1 of 3 chest pain clinics underwent CAC scoring. If the CAC score was 1000 or more Agatston units, interventional coronary angiography (ICA) was performed; if the CAC score was less than 1000, (computed tomography coronary angiography) CTCA was performed. All patients with a CAC score of 0 and low pretest likelihood of CHD had no obstructive CHD on CTCA and were event-free during follow-up. Of the 18 patients with CAC scores from 400 to 1000, 17 (94%) had greater than 50% obstruction on subsequent CTCA and were referred for further evaluation, 14 (78%) of whom had obstructive CHD. Of 15 patients with CAC scores 1000 or more and who were referred for coronary angiography, obstructive CHD was present in 13 (87%). This study suggested that CAC scoring can be used in the acute chest pain setting to stratify decision making for further testing.

(2013) Ten Kate et al. prospectively evaluated the accuracy of cardiac computed tomography (CT), including coronary artery calcium (CAC) scoring with or without computed tomography coronary angiography (CTCA), in distinguishing heart failure due to coronary artery disease (CAD) from heart failure due to non-CAD causes. Data on the predictive ability of a negative CAC score in ruling out CAD was also included. The study included 93 symptomatic patients with newly diagnosed heart failure of unknown etiology, all of whom underwent CAC scoring. Those with a CAC score greater than 0 underwent CTCA and, if the CTCA was positive for CAD (>20% luminal diameter narrowing), interventional coronary angiography (ICA) was recommended. Forty-six

percent of patients had a CAC score of 0. At a mean follow-up of 20 months, no patient with a CAC score of 0 had a myocardial infarction, underwent percutaneous coronary intervention, had a coronary artery bypass graft, or had signs of CAD.

Summary of Evidence

For individuals who are asymptomatic with risk of coronary artery disease (CAD) who receive coronary artery calcium (CAC) scoring as a stand-alone test, the evidence includes multiple systematic reviews, randomized controlled trials (RCTs) and nonrandomized observational studies. The role of CAC scoring, particularly for determining its incremental value for risk stratification in those with intermediate Framingham Risk Score (FRS) continues to be studied. Although randomized controlled trials and observational studies suggest that CAC scores may predict risk for future coronary events, the evidence shows variability in the accuracy of tests results. Data from the MESA trial was used to conclude that adding the CAC to the risk estimator resulted in a better prediction of ASCVD events. However, the problem is many people do not have ASCVD events and the number of people reclassified incorrectly is much higher than the number reclassified correctly. An AHRQ systematic review in 2018 for the U.S. Preventive Services Task Force does not offer recommendations for coronary artery calcium screening due to insufficient evidence. The 2018 recommendation for cardiovascular disease risk assessment with nontraditional risk factors that include coronary artery calcium (CAC) score, found inadequate evidence to assess whether treatment decisions guided by coronary artery calcium (CAC) score results, when added to existing CVD risk assessment models, lead to reduced incidence of CVD events or mortality. Also, direct evidence of improved patient outcomes from changes in statin, aspirin, and other preventive therapies prescribed according to CAC score is limited mainly to small- randomized studies and observational data. It is also important to note that according to a meta-analysis of four prospective studies statins do not appear to significantly reduce the rate of CAC progression. High-quality evidence demonstrating that the use of CAC scores in clinical practice leads to changes in patient management or in individual risk behaviors that improve cardiac outcomes is lacking. While some studies suggest that coronary artery calcium measurement may be a superior risk stratification method, it remains unclear whether coronary artery calcium scanning has a favorable effect on long-term clinical outcomes or decision making.

For coronary artery calcium (CAC) scoring alone as a primary diagnostic tool in a symptomatic individual concerning for myocardial ischemia, the evidence includes prospective and retrospective nonrandomized studies, systematic reviews and observational studies. In symptomatic patients a CAC score of 0 may not carry the same negative predictive value (NPV) as it does in asymptomatic patients. Among symptomatic individuals in the multicenter PROMISE study, coronary CTA was superior to CAC scoring for event prediction, with 16 percent of patients with CAC = 0 shown to have non-calcified plaque on coronary CTA. During approximately two years of follow-up, 16 percent of all events occurred in those with CAC = 0. While the absence of CAC may reduce the likelihood for coronary plaque and coronary artery stenosis, CAC as a

stand-alone test in symptomatic patients suggestive of myocardial ischemia may not be recommended due to the decreased specificity of CAC for predicting significant CAD and the high background prevalence of CAC that would necessitate additional testing. High-quality evidence demonstrating that the use of CAC scores in clinical practice leads to changes in patient management or in individual risk behaviors that improve cardiac outcomes is lacking.

Potential harms from coronary artery calcium (CAC) testing include radiation exposure, incidental findings in up to 40% of scans, misdiagnosis, downstream testing and costs. only moderate gain provided by CAC scores is often outweighed by the risks associated with CAC testing. Although experts do not recommend that coronary artery calcium (CAC) tests should start a cascade of downstream testing, it is routinely seen in asymptomatic individuals referred to stress testing, which often leads to coronary angiography and interventions. It is likely that most interventions that result from coronary artery calcium testing represent over treatment and incur potential harm. Moreover, recent studies have noted CACS appears to add some further discrimination to the traditional CVD risk assessment equations used but which individuals would benefit remains unclear. At present, limited to no evidence suggests that adding CACS to traditional risk scores provides clinical benefit.

The use of cardiac CT coronary artery calcium (CAC) scoring has not been conclusively shown to impact individual outcomes and therefore, is considered to be not medically necessary in all clinical situations.

Regulatory Status
Many models of CT devices, including EBCT and other ultrafast CT devices, have been cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process.

Practice Guidelines and Position Statements

American College of Cardiology (ACC)/American Heart Association (AHA)
(2019) The American College of Cardiology (ACC)/American Heart Association (AHA) released guideline on the *primary prevention of cardiovascular disease* that included the following recommendations:

- For individuals with intermediate predicted risk (≥ 7.5% to <20%) by the Pooled Cohort Equation (PCE) or for select adults with borderline (5% to < 7.5%) predicted risk, coronary artery calcium measurement can be useful tool in refining risk assessment for preventative interventions (e.g., statin therapy).
- Coronary artery calcium (CAC) might also be considered in refining risk for selected low risk adults (<5% 10-year risk), such as those with a strong family history of premature coronary heart disease (CHD).

- Coronary artery calcium (CAC) may refine ASCVD risk estimates among lower risk (<5%) younger adults (< 45 years) and older adults (>75 years) of age, but more data are needed to support its use in these subgroups.
- Coronary artery calcium measurement is not intended as a "screening" test for all but rather may be used as a decision aid in select adults to facilitate the clinician-patient discussion.

(*Accessed June 2022*)

(2021) The American College of Cardiology (ACC) / American Heart Association (AHA) released joint guidelines for the *Evaluation and Diagnosis of Chest Pain* which includes the following recommendations:

- Sequential or Add-on Testing: What to Do if Index Test Results are Positive or Inconclusive
    - For intermediate-high risk patients with stable chest pain and no known CAD undergoing stress testing, the addition of CAC testing can be useful.

(*Accessed June 2022*)

American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA)

(2010) The American College of Cardiology Foundation and the American Heart Association, issued a guideline for the *assessment of cardiovascular risk in asymptomatic adults*, which included the following recommendation regarding computed tomography for coronary artery calcium (CAC) scoring:

- Class IIa recommendation: Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10- year risk). (Level of Evidence: B)
- Class IIb recommendation: Measurement of CAC may be reasonable for cardiovascular risk assessment in persons at low to intermediate risk (6% to 10% 10- year risk). (Level of Evidence: B)
- Class III recommendation: No Benefit. Persons as low risk (<6% 10- year risk) should not undergo CAC measurement for cardiovascular risk assessment. (Level of Evidence: B)

(*Accessed June 2022*)

U.S. Preventative Services Task Force (USPSTF)

(2018) The U.S. Preventative Services Task Force (USPSTF) updated their 2009 recommendation regarding cardiovascular disease: risk assessment with non-traditional risk factors.

- The USPSTF concludes that current evidence is insufficient to assess the balance of benefits and harms of adding ankle-brachial index (ABI), high-sensivity 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.

Cardiovascular disease risk assessment in the United States has been generally based on the Framingham Risk Score and, more recently, the Pooled Cohort Equations (PCE). 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 USPSTF found only 1 study that directly assessed the potential benefit on clinical outcomes of adding 1 of these 3 nontraditional risk factors (ABI, hsCRP level, and CAC score) to traditional risk assessment models. 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. 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 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 benefit in CVD outcomes at 7 years of follow-up. 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. 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.

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

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**
  - 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 (i.e., 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.

PRIOR APPROVAL

Not applicable.

POLICY

Coronary artery calcium (CAC) scoring detection by means of computed tomography (CT) (electron beam computed tomography [EBCT], helical computed tomography or multi-slice spiral CT [MSCT]) is considered **not medically necessary** for all indications, because the use of cardiac computed tomography (CT) coronary artery calcium (CAC) scoring has not been conclusively shown to impact net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 75571 Computed tomography, heart, without contrast material, with quantitative evaluation of coronary calcium
- S8092 Electron beam computed tomography (also known as ultrafast CT, cine CT)

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POLICY HISTORY

Date	Reason	Action
July 2022	Annual Review	Policy Revision
July 2021	Annual Review	Policy Renewed
July 2020	Annual Review	Policy Revised
July 2019	Annual Review	Policy Renewed
July 2018	Annual Review	Policy Renewed
July 2017	Annual Review	Policy Revised
July 2016	Annual Review	Policy Revised
August 2015	Annual Review	Policy Revised
September 2014	Annual Review	Policy Revised
October 2013	Annual Review	Policy Revised
November 2012	Annual Review	Policy Renewed
November 2011	Annual Review	Policy Renewed
November 2010	Annual Review	Policy Renewed

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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