

Computed Tomography to Detect Coronary Artery Calcification

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Next Review: November 2021

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

CT scan-derived coronary artery calcium (CAC) measures allow the quantification of calcium in coronary arteries and have been used to evaluate coronary atherosclerosis.

MEDICAL POLICY CRITERIA

The use of computed tomography to detect and quantify coronary artery calcification is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. [Ultrasonographic Measurement of Carotid Artery Intima-Media Thickness as an Assessment of Atherosclerosis](#), Radiology, Policy No. 37
2. [Whole Body CT Screening](#), Radiology, Policy No. 40

BACKGROUND

Several types of fast computed tomography (CT) imaging, including but not limited to, electron beam computed tomography (EBCT), spiral computed tomography, and multi-detector

computed tomography (MDCT) have been used to quantify calcium in coronary arteries. A fast CT study for coronary artery calcium is a noninvasive measurement which generally takes 10 to 15 minutes and requires only a few seconds of scanning time.

Coronary calcium is present in coronary atherosclerosis, but the atherosclerosis detected may or may not be causing ischemia or symptoms. Coronary calcium measures may be correlated with the presence of critical coronary stenoses or serve as a measure of the patient's proclivity toward atherosclerosis and future coronary disease. Thus, it could serve as a variable to be used in a risk assessment calculation for the purposes of determining appropriate preventive treatment in asymptomatic patients. Alternatively, in other clinical scenarios, it might help determine whether there is atherosclerotic etiology or a component to the presenting clinical problem in symptomatic patients, thus helping to direct further workup for the clinical problem. In this second scenario, a calcium score of zero usually indicates that the patient's clinical problem is unlikely to be due to atherosclerosis and that other etiologies should be more strongly considered. CAC testing does not determine a specific diagnosis. Most clinical studies have examined the use of coronary calcium for its potential use in estimating the risk of future coronary heart disease (CHD) events.

Coronary calcium levels can be expressed in many ways. The most common method is the Agatston score, which is a weighted summed total of calcified coronary artery area observed on 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. Different imaging methods and protocols will produce different values based on the specific algorithm used to create the score.

REGULATORY STATUS

Many models of CT devices have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. Marketing clearance via the 510(k) process does not require evidence of clinical efficacy. FDA product code: JAK.

NOTE: This policy does not address the use of contrast-enhanced computed tomography angiography (CCTA) for coronary artery evaluation.

EVIDENCE SUMMARY

This policy addresses the use of CT for CAC scoring in asymptomatic individuals and CAC for evaluating atherosclerotic etiology of disease in symptomatic patients.

Assessment of the proposed uses of CT must fulfill three parameters:

1. Establish technical feasibility, typically assessed with two types of studies, those that compare test measurements with a gold standard and those that compare results taken with the same device on different occasions (test-retest). Normally conducted in the pre-clinical setting, the focus of this parameter is on test reproducibility and establishment of the test protocol.
2. Demonstrate diagnostic performance (sensitivity, specificity, positive and negative predictive values) of the test compared with the gold standard.
3. Evaluate clinical outcomes based on the performance of the test versus the standard of care. While in some cases, new diagnostic tests can be adequately evaluated using technical and diagnostic performance, when a test identifies a new or different group of

patients with a disease, randomized trials are needed to demonstrate the impact of the test on net health outcomes (balance of benefits and harms).

CORONARY ARTERY CALCIUM SCORING IN ASYMPTOMATIC INDIVIDUALS

Clinical Validity

A study published by Blaha (2019) evaluated the risk of all-cause and cardiovascular mortality in the subset of patients from the Coronary Artery Calcium Consortium that had CAC score of 0 (45% of the total 66,363 individuals in the study, mean age 45).^[1] After a mean follow-up of 12 years, these patients had very low rates of both all-cause, and CVD mortality (1.38 to 1.62 and 0.32 to 0.43 per 1,000 person-years, respectively). The authors suggested that patients with CAC scores of 0 may be candidates for more flexible treatment goals related to primary prevention.

Lee (2017) conducted a long-term study comparing the efficacy of risk prediction models using CCTA in 933 asymptomatic patients with type 2 diabetes with traditional risk factor models.^[2] Of the 94 patients with major cardiac events (MACE) who exhibited obstructive CAD, the performance of a risk prediction model was significantly improved (C index 0.788, 95% CI 0.747 to 0.829, $p=0.035$) by adding CCTA to traditional risk factors. The risk prediction model using the CAC score remained unimproved (C index 0.740, $p=0.547$). Small sample size, the lack of a standardized protocol for conducting coronary angiograms and/or percutaneous coronary interventions and medications after CCTA, and the uniformly high-risk characteristics of the study population limit conclusions to be drawn from this observational study.

Takamura (2017) retrospectively evaluated the incremental prognostic value of adding CCTA to plaque findings in 339 asymptomatic patients.^[3] Framingham Risk Score (FRS), CAC score, and CT-verified high-risk plaque were the standard predictors of cardiac events investigated; CT-verified high-risk plaque results were based on CCTA findings. Using multivariate Cox proportional hazard analysis, the authors determined that both CAC score (hazard ratio [HR] 13.23, 95% CI 1.62 to 107.78, $p<0.016$) and CT-verified high-risk plaque (HR 11.27, 95% CI 1.24 to 102.12, $p<0.032$) independently predicted cardiac events. Using net reclassification indices (NRI) and integrated discrimination improvement (IDI) reclassification, the authors calculated the improvement in predictive accuracy by adding CT-verified high-risk plaque findings. The NRI was 0.9556 ($p<0.001$) and IDI was 0.2582 ($p<0.020$), which suggested that the addition of CT-verified high-risk plaque improved the diagnostic performance of the CAC score and FRS. The retrospective design, inability to follow all patients, inability to clarify patient use of oral medications, small number of cases, and paucity of cardiac events are the limitations of this study.

Ferencik (2017) evaluated whether the distribution of CAC in individual coronary arteries and segments, as well as CAC in the proximal dominant coronary artery, as detected by cardiac CT predicts incident major CHD events independent of traditional CAC score in 1,268 asymptomatic subjects without prevalent major CHD from the offspring and third generation cohorts of the Framingham Heart Study.^[4] Results revealed a total of 42 major CHD events occurring during a median follow-up period of 7.4 years. Both the number of coronary arteries with CAC (HR 1.68 per artery, 95% CI 1.10 to 2.57, $p=0.02$) and the presence of CAC in the proximal dominant coronary artery (HR 2.59, 95% CI 1.15 to 5.83, $p=0.02$) were associated with major CHD events after multivariable adjustment.

Gepner (2017) evaluated CVD, CHD, and stroke or transient ischemic attack (TIA) events to compare the use of CAC with carotid plaque scores to predict CVD events; the cohort study used data from the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based cohort of individuals without known CVD.^[5] After 11.3 years of follow-up among 4,955 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. The authors noted that there were limitations in the MESA study and that carotid ultrasound continues to be a noninvasive, inexpensive, radiation free diagnostic tool and therefore potentially more suitable in children and young adults.

Nakanishi (2016) conducted a study among 13,092 consecutive asymptomatic individuals without known CAD (mean age 58 years) clinically referred for a CAC scan between 1997 and 2011 at a university medical center; the study examined the predictive value of CAC for five- and 15-year mortality rates among men and women.^[6] CAC showed an incremental prognostic value over traditional risk factors among men at five 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 five years (AUC 0.650 vs 0.612, $p=0.065$) but was statistically significant at 15 years (AUC 0.690 vs 0.624, $p<0.001$). The authors noted study limitations including the fact it was single center and risk factors being self-reported. Additional studies are needed.

Choi (2016) conducted a prospective study to assess the interscan variability of CT for coronary calcium quantification using image acquisition with standard and reduced radiation dose protocols.^[7] A total of 200 consecutive patients underwent nonenhanced CT for coronary calcium quantification twice at a standard radiation dose and twice at a reduced radiation dose in randomized order. Each scan underwent reconstruction with both filtered back projection (FBP) and iterative reconstruction (IR). Interscan agreement with respect to Agatston categories for reduced-dose/IR protocol was 91% (95% CI 87% to 94%), with a κ value of 0.87 (95% CI 0.83 to 0.93). For standard-dose/FBP protocol, the agreement was 93% (95% CI 89% to 96%) with a κ value of 0.91 (95% CI 0.86 to 0.95), for standard-dose/IR protocol, the agreement was 92% (95% CI, 87% to 94%), with a κ value of 0.89 (95% CI 0.84 to 0.94); and for reduced-dose/FBP protocol, the agreement was 90% (95% CI 86% to 94%), with a κ value of 0.88 (95% CI 0.82 to 0.93).

Kavousi (2016) reported on the use of CAC for CVD risk stratification among low-risk women.^[8] The meta-analysis included data from 6,739 women in five large cohort studies: the Dallas Heart Study, the Framingham Heart Study, the Heinz Nixdorf Recall Study, the Multi-Ethnic Study of Atherosclerosis, and the Rotterdam Study. These women had a 10-year risk of atherosclerotic CVD (ASCVD) below 7.5% and a mean age range of 44 to 63 years. CAC was present in 36.1% of the participants and was associated with an increased risk of ASCVD (4.33 events per 1000 person-years, vs 1.41 events per 1000 person-years in those without CAC). Adding CAC to the traditional risk factors resulted in a small improvement to the C statistic (from 0.73, 95% CI 0.69 to 0.77; to 0.77, 95% CI 0.74 to 0.81) and a net reclassification index of 0.20 (95% CI 0.09 to 0.31). This study did not assess the clinical utility of using CAC for risk stratification.

Additional analysis of data from the MESA study found that CAC is associated with CHD events among individuals at either high or low CHD risk on the basis of traditional risk factors.^[9] Blaha (2016) used data from MESA to demonstrate that CAC scores of 0 were

associated with the highest reclassification in cardiovascular risk, compared with other risk markers (e.g., high-sensitivity C-reactive protein [hs-CRP]).^[10] Gibson (2014) used data from the MESA study to evaluate the association between CAC and incidence of cerebrovascular events, including all strokes and transient ischemic attacks (TIAs).^[11] Over an average of 9.5 years of follow-up, 234 cerebrovascular events occurred (3.5%). Having an elevated CAC was independently predictive of both cerebrovascular events and stroke (HR 1.70, 95% CI 1.24 to 2.35, $p=0.001$; HR 1.59, 95% CI 1.11 to 2.07, $p=0.01$, respectively). Arps (2019) published a modeling study that used data from the MESA study to explore the potential for CAC scoring to identify individuals at high risk for a cardiovascular event that might benefit from prophylactic rivaroxaban treatment.^[12] The predicted five-year number needed to treat to avoid such an event was 75 for those with a CAC of 100 to 299 and 45 for those with a CAC above 300.

Won (2015) conducted a single center cross-sectional study among 328 consecutive asymptomatic patients with type 2 diabetes mellitus who underwent coronary computed tomographic angiography (CTA) between January 2008 and December 2009 in a hospital in South Korea to evaluate the predictive value of CAC for obstructive coronary plaques (OCP) assessed by CTA.^[13] On the basis of a CAC score (CACS) of 0, 1 to 10, 11 to 100, and greater than 100, OCPs were found in 2%, 5%, 15%, and 36% of patients, respectively. On receiver operating characteristic curve analysis, the optimal cutoff CACS 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 CACS of 33 for OCPs were 30 and 98%, respectively. On multivariate logistic regression analysis, age (odds ratio [OR] 1.09), microalbuminuria (OR 3.43), current smoking (OR 3.93), and CACS greater than 33 (OR 15.85) were found to be independently associated with an increased risk for OCPs ($p<0.05$, respectively).

Many additional studies have reported that CAC scoring adds predictive information among asymptomatic subjects.^[9, 14-25] Pursnani (2015) used data from the offspring and third-generation cohorts of the Framingham Heart Study, including 2,435 statin-naïve individuals, to evaluate the association of CAC as a predictive factor (beyond typical risk factors) with incident cardiovascular disease (CVD).^[26] CAC scores of greater than 100 and greater than 300 were associated with increased risk of cardiac events in both statin eligible and noneligible subjects. Similarly, a study of 1,029 asymptomatic adults with at least one coronary risk factor, Greenland (2004) showed that a calcium score of greater than 300 predicted increased risk of cardiac events within Framingham risk categories.^[23] A study by Taylor (2005) examined the association of the FRS and calcium scores in a young military population (mean age 43 years).^[14] Although only nine acute coronary events occurred, calcium scores were associated with risk of events while controlling for the risk score. LaMonte (2005) also analyzed the association of calcium scores and CHD events in 10,746 adults.^[27] In this study, coronary risk factors were self-reported. During a mean follow-up of 3.5 years, 81 CHD events occurred. Similar to the other studies, the relationship between calcium scores and CHD events remained after adjustment for other risk factors.

Budoff (2013) evaluated the association of coronary calcium scores and CHD events during five years of follow-up in an analysis of 2,232 adults from the Multiethnic Study of Atherosclerosis (MESA), a prospective cohort study to evaluate cardiac risk factors and 3119 subjects from the Heinz Nixdorf RECALL (HNR; Risk factors, Evaluation of Coronary Calcium and Lifestyle Factors) study.^[28] An increasing Agatston score was associated with increased risk of CHD. In the MESA study compared with a CACS of 0, having a score greater than 400 was associated with CHD after adjusting for CHD risk factors (HR 3.31, 95% CI 1.12 to 9.8), as

was a score of 100 to 399 (HR 3.2, 95% CI 1.19 to 8.95). In the HNR study, the HR for CHD was 2.96 (95% CI 1.22 to 7.19). Lower CAC scores were not significantly associated with CHD after adjustment for other risk factors. Other studies^[19, 29-32] show similar findings. Additionally, the U.S Preventative Services Task Force (USPSTF) conducted a systematic review and found wide variation was reported in the estimates of the risk ratio for higher calcium scores.^[33] Higher quality studies had lower relative risks for a given difference in calcium score. Limitations of the five studies were the use of proxy measures to control for Framingham risk factors, or recruitment of self-selected participants. USPSTF concluded the following: "Although the eight included studies consistently reported statistically significant relative risks for coronary events with increasing CAC scores, no study uniformly met all three of the following conditions: addressed an intermediate-risk cohort, was population-based or free of selection bias, and appropriately measured or controlled for traditional risk factors."

Clinical Utility

Ajufo (2020) used data from the Dallas Heart Study to evaluate the potential use of CAC to guide use of aspirin therapy for primary prevention.^[34] The Dallas Heart Study is a multi-ethnic population-based cohort study, with deliberate oversampling of African American individuals, that includes 6,101 adults between age 18 and 65. The primary outcomes in the study were first bleeding events or first atherosclerotic CVD (ASCVD) events leading to hospitalization or death. Participant CAC scores were grouped into three categories (0, 1-99, and ≥ 100) and the effect of aspirin therapy was modeled based on data from a 2019 aspirin meta-analysis^[35]. Overall, both bleeding and ASCVD risks increased with CAC scores. For those with CAC scores < 100 , the risk of bleeding with aspirin outweighed the reduction in risk of ASCVD. There was a potential net benefit of aspirin therapy for individuals with CAC ≥ 100 with an intermediate 10-year risk of ASCVD (5-20%), or for individuals at high ($> 20\%$) 10-year risk of ASCVD regardless of CAC score.

Shreibati (2014) used Medicare claims data to compare clinical outcomes and cardiac testing utilization for patients who had CAC scoring with patients who had high-sensitivity C-reactive protein (hsCRP) testing or lipid screening.^[36] The study included 4,184 patients who had CAC who were propensity-score matched to 261,356 patients who had hsCRP and 118,093 patients who had lipid screening. CAC testing was associated with increased rates of noninvasive cardiac testing within 180 days (HR 2.22, 95% CI 1.68 to 2.93, $p < 0.001$ vs hsCRP; HR 4.30, 95% CI 3.04 to 6.06, $p < 0.001$ vs lipid screening). It was also associated with increased rates of coronary angiography (HR 3.54, 95% CI 1.91 to 6.55, $p < 0.001$ vs. hsCRP; HR 4.23, 95% CI 2.31 to 7.74, $p < 0.001$). Overall rates of the composite outcome of death, myocardial infarction, or stroke were low, but event-free survival was higher in patients who underwent CAC compared with those who had hsCRP (94.4% vs 92.7%, $p = 0.008$).

A number of studies have evaluated whether the use of CAC in asymptomatic patients is associated with subsequent behavioral change; particularly related to risk factor reduction or medication adherence. Gupta (2017) performed a systematic review and meta-analysis evaluating the odds of initiating or continuing pharmacological (i.e., aspirin, lipid-lowering, and blood pressure lowering medications) and lifestyle preventive therapies in asymptomatic CAD patients with nonzero versus 0 CAC scores as detected on cardiac CT.^[37] Results revealed that the odds of aspirin, lipid-lowering, and blood pressure lowering medication initiation, lipid-lowering medication continuation, an increase in exercise, and dietary changes were significantly higher in patients with nonzero CAC versus 0 CAC scores. However, the odds of aspirin or blood pressure-lowering medication continuation were not significantly increased in

the nonzero CAC group. Statistical heterogeneity was present across studies for many of the outcomes; potential sources of heterogeneity included variations in sample size and the proportion of patients with 0 versus nonzero CAC, whether patients were shown their CAC scan, and differences in clinical characteristics of study populations.

Mamudu (2014) conducted a systematic review of studies evaluating the effects of CAC screening on behavioral modification, risk perception, and medication adherence in asymptomatic adults, which included 15 studies, three RCTs, and 12 observational studies.^[38] The review primarily provided descriptive results of the studies given the lack of standardization across studies in terms of CAC measures and outcome variables. Thirteen of the 15 studies, including two of the RCTs, reported increased medication adherence in CAC-screened patients. An example of one of the observational studies included in the Mamudu (2014) review was reported by Johnson (2014), who assessed the association between CAC score and subsequent health behavior change.^[39] The study included a convenience sample of 174 adults with CHD risk factors who underwent CAC scoring. The authors found no significant change in risk perception measured by the Perception of Risk of Heart Disease Scale scores between groups (CAC score, 0, 1 to 10, 11 to 100, 101 to 400, and greater than 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.

Wheaton (2012) published a meta-analysis of RCTs that evaluated the impact of coronary calcium scores on cardiac risk profiles and cardiac procedures.^[40] There were four trials identified with a total of 2,490 participants; the individual trials ranged in size from 50 to 1934 patients. The authors pooled data from four trials on the impact of calcium scores on blood pressure, three on the impact on low-density lipoprotein, and two on the impact on high-density lipoprotein. Pooled analysis did not show a significant change in any of these parameters as a result of calcium scores. Similarly, in four studies that looked at the rates of smoking cessation following calcium scores, there was not significant change found. There were two studies that included rates of coronary angiography and two studies that included rates of revascularization. Pooled analysis of these studies did not show a significant change following measurement of coronary calcium. One of these studies, by O'Malley (2003), randomized 450 subjects to receive EBCT, or not, and assessed outcomes one year later for change in FRS.^[41] Thus, EBCT was used as a guide to refine risk in patients and possibly provide motivation for behavioral change. The study was not powered for clinical end points. EBCT did not produce any benefits in terms of a difference in Framingham risk score at one year.

Whelton (2011) evaluated the impact of CT scanning for CAC on cardiac risk factors.^[42] A total of 2,137 healthy subjects were randomized to CT scanning or no CT scanning and followed for four years. At baseline, both groups received one session of risk factor counseling by a nurse practitioner. The primary outcome was change in 12 different cardiac risk profile measures, including blood pressure, lipid and glucose levels, weight, exercise, and FRS. At the four-year follow-up, there was differential dropout among the groups, with 88.2% of follow-up in the scan group versus 81.9% in the no-scan group. Results demonstrated differences in four of the 12 risk factor measurements between groups: systolic blood pressure, low-density lipoprotein, waist circumference, and mean FRS. This trial highlights the potential benefit of CAC screening in modifying cardiac risk profile but is not definitive in demonstrating improved outcomes. Limitations of this study include different intensity of interventions between groups and differential dropout rates. It is possible that the small differences reported in the trial were the result of bias from these methodologic limitations. In addition, this trial does 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 given that this was a volunteer population that may have been highly motivated for change.

Additional studies have defined how the incorporation of calcium scores into risk scores changes risk prediction. In the study by Polonsky (2010) the incorporation of calcium score into a risk model resulted in more subjects (77% vs 66%) being classified in either high- or low-risk categories.^[17] The subjects who were reclassified to high risk had similar risk of CHD events as those who were originally classified as high risk. A study by Elias-Smale (2011) showed similar findings; reclassification of subjects occurred most substantially in the intermediate-risk group (five-year risk of 5% to 10%) where 56% of persons were reclassified.^[43]

Some studies have evaluated whether CAC score changes CHD risk prediction in addition to, or compared with, other types of noninvasive testing in conjunction with clinical risk scores. For example, Chang (2015) prospectively evaluated whether CAC score added incremental predictive value to exercise treadmill testing and stress myocardial perfusion single-photon emission CT testing in predicting risk of cardiac events.^[44] Cardiac events were defined as a composite of cardiac death, nonfatal myocardial infarction, and the need for coronary revascularization in a cohort of 988 asymptomatic or symptomatic low-risk patients without known CHD. Over a median follow-up of 6.9 years, the rate of cardiac events was 11.2% (1.6% per year). Annual event rates were higher in patients with CAC scores above 400 compared with those with CAC score of less than or equal to 10 (3.7% vs 0.6% per year, $p < 0.001$). The addition of CAC score to risk stratification based on FRS improved risk prediction.

Numerous studies have also evaluated the predictive ability of coronary calcium using CTA.^[45-50] These studies have included different populations, such as patients with or without risk factors or patients with an intermediate risk of CAD. Similar to studies that use EBCT, these studies have demonstrated that calcium scores derived from CTA provide incremental predictive information for the overall risk of CAD, as compared with coronary angiography and for the future occurrence of major cardiac events.

Section Summary

For individuals who are asymptomatic with risk of CAD who receive CAC scoring, the evidence includes systematic reviews, RCTs and, nonrandomized studies. There is evidence on the predictive value of CAC score screening for cardiovascular disease among asymptomatic patients that demonstrates scanning can predict risk of CAD. However, evidence from high quality studies that demonstrate the use of CAC score measurement in clinical practice leads to changes in patient management or changes in individual risk behaviors that improve cardiac outcomes is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

CORONARY ARTERY CALCIUM FOR EVALUATING ATHEROSCLEROTIC ETIOLOGY OF DISEASE IN SYMPTOMATIC PATIENTS

In certain clinical situations, such as patients presenting with chest pain or other symptoms, it is uncertain whether the symptoms are potentially due to CHD. Coronary calcium measurement has been proposed as a method that can rule out CHD in certain patients if the coronary calcium value is zero. Because coronary disease can only very rarely occur in the absence of coronary calcium, the presence of any coronary calcium can be a sensitive, but not specific, test for coronary disease. False positives occur because the calcium may not be

causing ischemia or symptoms. The absence of any coronary calcium can be a specific test for the absence of coronary disease and direct the diagnostic workup toward other causes of the patient's symptoms. In this context, coronary calcium measurement is not used to make a positive diagnosis of any kind but as a diagnostic tool to rule out an atherosclerotic cause for the patient's symptoms.

Lo-Kioeng-Shioe (2019) conducted a systematic review and meta-analysis of 19 observational studies (n=34,041) to assess the ability of CAC to predict risk of MACE, defined as the composite of late cardiac revascularization, hospitalization for unstable angina pectoris or heart failure, nonfatal myocardial infarction, and cardiac death or all-cause mortality) in stable patients with suspected CAD. Of 1,601 cardiovascular events, 158 occurred in patients with a CAC score of 0. The pooled risk ratio for MACE in patients with CAC >0 was 5.71 (95% CI 3.98 to 8.19), and risk increased with increasing levels of CAC. The pooled relative risk for incidence of all-cause mortality or nonfatal myocardial infarction was 3.64 (95% CI 2.68 to 4.96).

Chaikriangkrai (2016) published a systematic review that evaluated the use of CAC scoring in patients without known CAD presenting in the emergency department with acute chest pain.^[51] The review included eight longitudinal studies with a total of 3,556 patients and a median follow-up of 10.5 months. After pooling the studies for meta-analysis, the authors found that the prevalence of CACS of 0 was 60%, and that major adverse cardiovascular event (MACE) rates for individuals with CACS of 0 were significantly lower than for those with CACS greater than 0 (MACE 0.8% per year and death or myocardial infarction 0.5% per year, vs MACE 14.6% per year; death or myocardial infarction 3.5% per year, respectively). The authors conclude that initial testing with CACS could prevent further cardiac testing and unnecessary hospitalizations in those with a CACS of 0. A limitation of this meta-analysis is that the included populations do not represent all patients with acute chest pain presenting to the emergency department, as the studies all enrolled hemodynamically stable patients without ischemic ECG changes or increased cardiac markers. Additionally, several included studies were performed more than 15 years ago, and likely reflect temporal differences in treatment standards.

Studies that were not reported in the reviews above include a prospective study by Yerramasu (2014) assessing an evaluation algorithm including CAC scoring for patients presenting to a rapid access chest pain clinic with stable chest pain possibly consistent with CHD.^[52] Three hundred patients presenting with acute chest pain to one of three chest pain clinics underwent CAC scoring. If the CAC score was 1000 or more Agatston units, invasive coronary angiography (ICA) was performed, and if the CAC score was less than 1000, CTA was performed. All patients with a CAC of zero and low pretest likelihood of CHD had no obstructive CHD on CTA and were event-free during follow-up. Of the 18 patients with CAC score from 400 to 1000, 17 (94%) had greater than 50% obstruction on subsequent CTA and were referred for further evaluation, 14 (78%) of whom had obstructive CHD. Of 15 patients with CAC score 1000 or more and who were referred for coronary angiography, obstructive CHD was present in 13 (87%). This study suggests that CAC can be used in the acute chest pain setting to stratify decision making for further testing.

Williams (2015) assessed results from 210 CCTA from the Scottish Computed Tomography of the Heart (SCOT-HEART) trial to examine intraobserver and interobserver variability in determining CAC score.^[53] Patients in the SCOT-HEART trial were attending the rapid access chest pain clinic. There were no differences in Agatston calcium score on intraobserver assessment (373, 95% CI 224 to 505 Agatston units vs 278, 95% CI 202 to 354 Agatston

units, $p=0.138$) or interobserver assessment (290, 95% CI, 210 to 370] Agatston units; $p=0.191$). The authors used Bland-Altman plots to examine intraobserver and interobserver agreement. Excellent intraobserver and interobserver agreement was identified for CAC scores below 1000.

Korley (2015) reported a pilot study describing a diagnostic strategy of low high-sensitivity troponin I (hsTnI) and CAC to identify individuals at low risk of CAD presenting with suspected ACS, and in whom CCTA could be avoided.^[54] The authors report on 314 patients presented to an ED with suspected ACS. A strategy of avoiding any further testing in patients with an undetectable hsTnI but obtaining CAC in patients with detectable but non-increased hsTnI and CCTA in subjects with Agatston greater than 0 has NPV of 100.0% (95% CI 98.2% to 100%) for significant CAD.

Lubbers (2016) compared CAC scoring to functional testing in the CRESCENT trial, which randomized 350 patients with suspected coronary artery disease at four Dutch hospitals.^[55] There were 242 patients randomized to a tiered cardiac CT approach, and 108 patients randomized to standard care based on functional testing. The CT approach began with determination of a CAC score. Patients with a score of 1 to 400 then underwent CT angiography, while patients with a CAC score greater than 400 or an indeterminate CT angiogram underwent functional testing or invasive angiography. The functional test strategy involved exercise ECG testing and/or myocardial perfusion or stress echocardiography. After one year, fewer patients in the CT group reported angina than in the functional testing group (25% vs 39%), but the proportion of patients with similar or worsened symptoms were not significantly different. Event-free survival at 1.2 years was greater in the CT group as well. Interpretation of these results is limited by differing loss to follow-up between the two groups (22% for those in the functional testing group vs 14% in the CT group) and lack of long-term follow-up.

Ten Kate (2013) conducted a prospective study to evaluate the accuracy of cardiac CT, including CAC scoring with or without CTA, in distinguishing heart failure due to CAD from heart failure due to non-CAD causes.^[56] Data on the predictive ability of a negative CAC 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 of greater than zero underwent CCTA, and if the CCTA was positive for CAD (>20% luminal diameter narrowing), ICA was recommended. Forty-six percent of patients had a CAC score of zero. At follow-up of mean duration 20 months, no patient with a CAC score of zero had a myocardial infarction, underwent percutaneous coronary intervention, had a coronary artery bypass graft, or had signs of CAD.

Dharampala (2013) retrospectively evaluated a cohort of 1,975 symptomatic patients who underwent clinical evaluation and CAC scoring and CCTA or ICA.^[57] The primary outcome was obstructive CAD ($\geq 50\%$ stenosis) on ICA or CCTA (if ICA was not done). The authors evaluated the net reclassification improvement with the addition of CAC score to a clinical prediction model for patients who had an intermediate probability of CHD (10% to 90%) after clinical evaluation based on chest pain characteristic, age, sex, risk factors, and electrocardiogram. Discrimination of CAD was significantly improved by adding the CAC score to the clinical evaluation (area under the curve, 0.80 vs 0.89, $p<0.001$).

Section Summary

A number of studies suggest that CAC scoring could be used to rule in or rule out CHD, particularly regarding decisions about further invasive imaging. However, relatively few studies have employed a prospective design. Moreover, studies need to be conducted to address some of the potential barriers to such an approach, including whether performing CAC scoring in symptomatic patients delays diagnosis or intervention and whether the net effect of CAC scoring is to increase or decrease invasive testing.

PRACTICE GUIDELINE SUMMARY

U.S. PREVENTIVE SERVICES TASK FORCE (USPSTF)

The U.S. Preventive Services Task Force (2018) updated its recommendations on the use of nontraditional or novel risk factors in assessing coronary heart disease risk in asymptomatic persons.^[58] Calcium score was one of three nontraditional risk factors considered. Reviewers concluded that the current evidence was insufficient to assess the balance of benefits and harms of adding any of the nontraditional risk factors studied to traditional risk assessment for cardiovascular disease in asymptomatic persons.

AMERICAN COLLEGE OF CARDIOLOGY (ACC) AND THE AMERICAN HEART ASSOCIATION (AHA)

The AHA/ACC (2019) issued a special report on the use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic CVD.^[59] The guidelines include an algorithm of clinical approaches to incorporate CAC measurement in risk assessment for borderline- and intermediate-risk patients:

"For borderline-risk (10-year risk 5% to <7.5%) and intermediate-risk (7.5% to <20%) patients who are undecided regarding statin therapy, or when there is clinical uncertainty regarding the net benefit, consider the value of additional testing with measurement of CAC. If CAC is measured, interpret results as follows:

- a. CAC score of 0 indicates that a borderline- or intermediate-risk individual is reclassified to a 10-y event rate lower than predicted, and below the threshold for benefit from a statin. Consider avoiding or postponing statin therapy unless there is a strong family history of premature ASCVD, history of diabetes mellitus, or heavy cigarette smoking. Consider repeat CAC measurement in 5 years if patient remains at borderline or intermediate risk.
- b. CAC score 1 to 99 and <75th percentile for age/sex/race/ethnicity indicates that there is subclinical atherosclerosis present. This may be sufficient information to consider initiating statin therapy, especially in younger individuals, but does not indicate substantial reclassification of the 10-y risk estimate. Consider patient preferences and, if statin decision is postponed, consider repeat CAC scoring in 5 years.
- c. CAC score 100 or >75th percentile for age/sex/race/ethnicity indicates that the individual is reclassified to a higher event rate than predicted, that is above the threshold for statin benefit. Statin therapy is more likely to provide benefit for such patients."

The ACC/AHA (2018) Clinical Practice Guidelines on the Management of Blood Cholesterol state, "When risk status is uncertain, a CAC score is an option to facilitate decisionmaking in adults 40 to 75 years of age."^[60] The guidelines further note, "One purpose of CAC scoring is

to reclassify risk identification of patients who will potentially benefit from statin therapy. This is especially useful when the clinician and patient are uncertain whether to start a statin. Indeed, the most important recent observation has been the finding that a CAC score of 0 indicates a low ASCVD risk for the subsequent 10 years. Thus, measurement of CAC potentially allows a clinician to withhold statin therapy in patients showing 0 CAC."

With regard to the prognostic significance of CAC, the guideline "makes use of the available data to predict the risk associated with CAC."^[60] The guideline notes that "these data need to be amplified by new and ongoing studies to guide treatment decisions" and that "particular uncertainty exists about the predictive value of intermediate CAC scores." Additionally, there are concerns regarding the predictive significance of a CAC score of 0, which must be further verified in follow-up studies. For patients with a 0 score, "it is currently uncertain when and if follow-up CAC measurements should be done to reassess risk status."

The ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease (2019) is in line with the blood cholesterol guideline stating that adults (40 to 75 years of age) who are being evaluated for cardiovascular disease prevention should initially undergo 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimation with a clinician-patient risk discussion before starting pharmacological therapy.⁴^[61] The guideline also notes that assessing for other risk-enhancing factors can help guide decision making "about preventive interventions in select individuals, as can CAC scanning." The guideline specifically states the following recommendation regarding assessment of cardiovascular risk and CAC:

"In adults at intermediate risk ($\geq 7.5\%$ to $< 20\%$ 10-year ASCVD risk) or selected adults at borderline risk (5% to $< 7.5\%$ 10-year ASCVD risk), if risk-based decisions for preventive interventions remain uncertain, it is reasonable to measure a CAC score to guide clinician-patient risk discussion [Class (Strength) of Recommendation: IIa; Level (Quality) of Evidence: B-NR]. A IIa class of recommendation is of moderate strength based on moderate quality nonrandomized studies."

ACC/AHA/AATS/PCNA/SCAI/STS

In 2012, ACC/AHA/AATS/PCNA/SCAI/STS published guidelines for the diagnosis and management of patients with stable ischemic heart disease that include some recommendations related to CAC scoring^[62]:

- Class IIb recommendation: For patients with a low to intermediate pretest probability of obstructive IHD, noncontrast cardiac computed tomography to determine the coronary artery calcium score may be considered. (Level of Evidence: C)

Level C evidence is defined as: For certain conditions for which inadequate data are available, recommendations are based on expert consensus and clinical experience.

In 2014 ACC/AHA/AATS/PCNA/SCAI/STS issued a focused update to the 2012 guideline on the diagnosis and management of patients with stable ischemic heart disease with no additional recommendations related to CAC scoring.^[63]

AMERICAN COLLEGE OF PREVENTIVE MEDICINE (ACPM)

The 2011 ACPM position statement on ASCVD screening in adults states that the ACPM does not recommend routine screening, including EBCT, of the general adult population.^[64] The

statement also notes a lack of evidence that coronary calcium scores improve the prediction of CHD in populations at intermediate risk, stating that more population-based studies are needed in the intermediate risk population.

SUMMARY

It appears that coronary artery calcium (CAC) score may improve cardiovascular disease risk prediction for some people. More research is needed to know for sure. Therefore, the use of computed tomography to detect and quantify coronary artery calcification is considered investigational.

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CODES

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

Date of Origin: January 1996