Title

Coronary artery calcium score: pivotal role as a predictor for detecting coronary artery disease in symptomatic patients.

Journal

Coronary artery disease, 32(6)

ISSN

0954-6928

Authors

Cherukuri, Lavanya
Birudaraju, Divya
Budoff, Matthew J

Publication Date

2021-09-01

DOI

10.1097/mca.0000000000000999

Peer reviewed

TITLE: Coronary artery calcium score: Pivotal role as a predictor for detecting coronary artery disease in symptomatic patients

Authors: Lavanya Cherukuri, Divya Birudaraju, Matthew J Budoff.

Abstract:

Chest pain and dyspnea are common presentations for symptomatic individuals with suspected CAD in the primary care office and cardiology clinics. However, it is imperative to properly diagnose who should undergo further evaluation for cardiac etiologies of chest pain, with either non-invasive or invasive imaging tests. The purpose of this review is to highlight the role of coronary artery calcium (CAC) score as a screening tool for symptomatic patients to detect CAD. The purpose of CAC scoring is to establish the presence and severity of coronary atherosclerosis and can play a vital role in symptomatic patients. The use of CAC testing in symptomatic patients has traditionally been limited due to fundamental concerns including the occurrence of coronary calcification relatively late in the atherosclerotic process and high prevalence of CAC in the population. Further issue relate to its low specificity for obstructive CAD, as well as demonstration of significant ethnic variability in plaque composition and calcification patterns.

CAC testing as gained attention as an inexpensive, rapid, reproducible and a safe alternative to exclude CAD in symptomatic patients and defer further invasive imaging tests. This paper will review the available literature in regards to use of CAC in symptomatic populations.

Introduction:

Coronary artery disease (CAD) is a leading cause of cardiovascular mortality accounting for 42.6% of all such deaths followed by stroke (17%).(1) For the past few decades, the pretest probability (PTP) of obstructive CAD was assessed based upon symptom presentation and known cardiovascular (CV) risk factors such as hypertension, hyperlipidemia, family history of CAD, and

smoking.(2,3) These risk factor assessment scores predict only 65-80% of future cardiac events, which leads to many individuals experience a major adverse cardiac events (MACEs) despite being classified as low risk by means of traditional risk factors.(4,5)

The presence of calcium in the coronary arteries correlate strongly with the presence and severity of coronary atherosclerosis, as confirmed by histopathology and intravascular ultrasound studies (IVUS).(7,8) Non-invasive evaluation of symptomatic individuals to rule out acute coronary syndrome (ACS) using a high reliable consistent screening technique remains a clinical challenge. Several studies have demonstrated the efficiency of coronary artery calcium (CAC) to predict the CV events in asymptomatic patients, independent of conventional risk factors(9) and is recommended as a first-line examination in lower risk patients with stable chest pain symptoms to rule out coronary atherosclerosis by 2010 National Institute for Health and Clinical Excellence (NICE) guidelines. However, there was a considerable controversy and limitations for the use of CAC testing in symptomatic patients. In this review, we intend to review the role of CAC in symptomatic patients with supporting evidence and emphasizing the challenges for its widespread application based on the most significant research articles.

Symptomatic individuals with pre-test probability of CAD

Chest pain and dyspnea are common presentations for symptomatic individuals with suspected CAD in the primary care office and cardiology clinics. Acute chest pain is one of the most common symptoms in patients presenting to emergency department(ED), accounting for approximately 5-6 million ED visits and 1 in every 50 outpatient visits in the US.(6) The vast majority of these are discharged with non-cardiac diagnosis (about 55%). However, due to the high morbidity and mortality of CAD, most patients undergo non-invasive/invasive cardiac imaging to better determine individual CV risk. This ultimately imposes an enormous burden on the annual healthcare costs and remains a challenge for physicians to evaluate the patients with the most adequate diagnostic approach to stratify CV risk.

Determining the PTP of CAD based on the key parameters from the clinical history is a fundamental component in the initial evaluation of symptomatic patients with suspected CAD which directly influences the decision for noninvasive diagnostic testing and treatment.(7) To assist the clinician and to provide a clinical insight into the risk for cardiovascular complications, Coronary Artery Surgery Study (CASS) Registry,(8) Diamond and Forrester, (3) and Pryor and colleagues(9) have shown the prevalence of angiographically significant CAD based on age, sex, and angina typicality. Reeh et al.(10) demonstrated that prevalence of obstructive CAD is < 5% in patients with PTP< 15% and they recognized the performance of diagnostic testing among the patients with PTP 5-15% is more closely reflects current clinical practice and particularly with atypical symptoms which need further clarification. However, this study estimated the clinical likelihood of CAD risk by using the new PTPs based on age, gender, the nature of symptoms and presence of cardiovascular risk factors (such as family history of CVD, dyslipidemia, diabetes, hypertension, smoking, and other lifestyle factors). In a Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, 50% intermediate likelihood of obstructive CAD patients were reclassified to a PTP< 15% according to Reeh at al. PTP.(11)

Functional and anatomical cardiac testing in symptomatic patients

The screening or diagnostic tests should provide information about the absence or presence of CAD, and preferable the extent of the CAD. Since most of the symptomatic patients will have another cause for their symptoms such as pulmonary, gastric or myogenic, it is important to excluded CAD by non-invasive imaging.

Functional Testing: Functional cardiac testing (exercise electrocardiography (ECG), exercise/pharmacologic stress echocardiography, exercise/pharmacologic cardiac nuclear imaging with SPECT or PET, and pharmacologic stress MRI) has been a preferred algorithm for evaluation of stable chest pain to identify the patients with ischemia before invasive coronary

angiography (ICA). These diagnostic modalities are readily available in the clinical setting and ED for risk stratification in patients presented with angina like symptoms. However, all those have significant limitations. Resting 12-lead ECG lacks adequate sensitivity and negative predictive, (12,13) and exercise ECG is a useful tool only in ambulatory patients for the detection of CAD. (14,15) Resting 2-D echocardiography (echo) has low sensitivity to predict cardiac events in patients with possible ACS (16) whereas, stress echo requires experienced technicians and readers with good image quality to maintain diagnostic accuracy and reproducibility (17).Single photon-emission CT(18) and perfusion imaging(19) are not ideal for initial evaluation and to rule out ACS for several reasons including cost, substantial exposure to radiation, time to perform a test and required a trained technician. After functional testing (FT), majority of the symptomatic patients were later found to have non-obstructive CAD or normal coronary arteries on ICA.(7) Because of this diagnostic inefficiency of Functional Testing, assessment of symptomatic patients is not targeted for the detection of CAD, instead the assessment is focused on the risk stratification of patients to reduce the healthcare cost and need for unnecessary invasive procedures..

Anatomical testing: Evaluation of symptomatic patients by assessing CAC score and coronary plaque burden has a significant impact in clinical practice. This might enhance the efficacy of early detection of coronary stenosis in the assessment of acute chest pain.(17) However, CCTA entails the risk of contrast nephropathy, radiation exposure and moreover the test is not easily affordable by many.(18) The use of iodine contrast and drugs such as β- blockers or nitrates may cause bradycardia. High heart rate (HiHR), arrhythmias and obesity could affect image quality and reduce its accuracy. CAC score is less affected by motion artifacts due to HiHR and arrhythmias. This provides an edge for easy-to-use and less invasive tests such as CAC scoring for risk stratification of subjects with chest pain and risk of CAD to reduce the need for expensive and invasive procedures without needles, contrast or β - blockers or nitrates.

Cardiac computed tomography (CT) is the most established non-invasive imaging technique for CAC detection and is a non-contrast, limited chest CT acquired with an ~3-5s breath hold. Recent advancements in the cardiac imaging modalities and its clinical application, multidetector CT (MDCT) provides high image quality with spatial temporal resolution, soft based motion correction and usually takes 10-15mins at ≥ 1mSv of radiation. Coronary calcium is defined as a lesion of at least 1 mm^2 with >130 Hounsfield Units (HU) or ≥3 adjacent pixels and the original calcium score was developed by Agatston et al.(20). Agatston score is determined as a product of the calcified plaque area and maximal calcium lesion density from 1 to 4 based on Hounsfield units. The standardized methods have been used to relate the CAC score and coronary plaque burden as shown in Table 1.

Table 1: Calcium score interpretation.

CAC score (Agatston units)	**Presence of atherosclerotic plaque**	**Risk of coronary artery disease (CAD)**
0	No identifiable atherosclerotic plaque	Very low, < 5%
1-10	Minimal plaque burden	Very unlikely, < 10%
11-100	Mild plaque burden	Mild or minimal coronary stenosis
100-399	Moderate plaque burden	Moderate non-obstructive CAD highly likely
≥ 400	Extensive plaque burden	Higher likelihood of atleast one significant coronary stenosis (> 50%)

CAC testing and Functional testing: CAC testing (sensitivity, 90%; specificity, 85%) compares well with exercise ECG testing (sensitivity, 68%; specificity, 77%), single-photo emission CT myocardial perfusion imaging (sensitivity, 88%; specificity, 77%), and stress echocardiography (sensitivity, 76%; specificity, 88%). (21) Lubbers et al.(22) Evaluated the sequential testing algorithm in a prospective randomized trial that used CAC as a first-line test, advancing to CTA when CAC scores were 1 to 400. The event-free survival was demonstrated in 96.7% for patients randomized to CT and 89.8% for patients randomized to FT (P<0.011). Additionally, CT approach established diagnosis sooner than FT (P<0.0001), resulting in less downstream testing (25% versus 53%; P<0.0001) and lower cumulative diagnostic costs (€369

versus €440; P<0.0001). Lubbers and colleagues concluded that "Incorporating the calcium scan into the diagnostic workup was safe and lowered diagnostic expenses and radiation exposure." In a recent prospective trail, the prognostic value of CAC compared to functional stress testing among stable patients with suspected CAD was investigated. In that trial, most patients who experienced clinical events presented with positive (CAC > 0) CAC scans and only a minority exhibited abnormal functional stress test.(11)

Guidelines for CAC testing in symptomatic individuals

Previous studies have shown the CAC score as an effective filter for CTA/ invasive angiogram to diagnose a significant CAD in patients presenting with chest pain. Based on such data, a 2007 ACC/AHA expert consensus statement(2) and 2010 UK-based National Institute for Health and Clinical Excellence (NICE) guidelines(23) endorsed CAC testing as a first line test for symptomatic patients with a low PTP of obstructive CAD (10–29 %) by modified Diamond-Forrester (DF) score. According to the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes, CAC testing is recommended in symptomatic patients with PTP 5-15% to determine the clinical likelihood of obstructive CAD.(27) Calcium score of zero obtained by cardiac CT is associated with a low prevalence of obstructive CAD (<5%) and low risk of death or nonfatal MI (< 1%). Furthermore, 2019 ACC/ AHA guidelines on cholesterol management to reduce the atherosclerotic cardiovascular risk in adults suggest coronary artery calcium (CAC) score may be considered to guide statin therapy after quantitative risk assessment using traditional risk factors.(24)

All these above guidelines rely on the PTP of CAD. More controversially, in 2016 NICE guidelines update made three major changes to the 2010 version.(25) The first recommendation is to remove the PTP model for a clinical assessment of the likelihood of CAD, and the use of CTCA as the first-line investigation in all patients with atypical or typical angina symptoms or those who are asymptomatic with suggested EKG changes for ischemia. The second change is that calcium score of zero in patients with low PTP is no longer used to rule out CAD. Thirdly, CCTA should be

considered as a first line test for all stable chest pain patients based on their cost-effectiveness analysis suggesting that this would be a lower cost strategy. For instance, the PROMISE Trial enrolled 10,003 symptomatic patients with low-intermediate disease prevalence population with only 11% having CAD and reported the similar clinical outcomes among the patients evaluated by CCTA and functional tests (exercise electrocardiography, nuclear stress testing, or stress echocardiography) over a median follow-up of 2years. (26) Although, SCOT-HEART trial enrolled patients with high prevalence of CAD and demonstrated the diagnostic ability of CCTA when added to the standard-of-care (SOC). Exercise ECG was used as a SOC in SCOT-HEART trail but not any functional imaging tests or CAC testing.(27) There is little or no clinical data available supporting the NICE recommendations for CCTA demonstrating the diagnostic accuracy or cost effectiveness over other noninvasive imaging tests in population with low-intermediate risk of CAD. Furthermore, it increases the need for radiographers and consultants to perform and report the additional CCTA.

The ability of CAC score to rule out obstructive CAD in symptomatic patients

CCTA had been demonstrated to have high discriminatory ability for CAD compared to both CAC and FT.(11) CAC testing is recommended to use in a binary fashion (CAC present or absent) so that those without CAC may avoid further evaluation of obstructive CAD and those with any CAC (CAC>0) receive additional testing. Even though the CAC score showed a significant correlation with the severity of CAD, the CAC> 0 itself cannot differentiate between obstructive and non-obstructive CAD. Therefore, there is a considerable controversy for its use in symptomatic patients and the prevalence of obstructive CAD with CAC=0 strongly depends on the study population.(28) There is a great clinical value when CAC applied in selected patient populations.

CAC is an effective initial tool to risk stratify the low to intermediate risk patients with possible angiographically

significant CAD on the basis of its high negative predictive value and sensitivity.(29,30) Fernandez-Friera et al.(31) determined the diagnostic value of CAC to detect the obstructive CAD among 225 patients with possible ischemic chest pain and thrombolysis in myocardial infarction (TIMI) scores <4 (OR= 7.01; p = 0.02). Calcium score of zero were reported in 133 patients (59%) and 2 patients (2/133=1.5%) have obstructive CAD on CCTA with 99% NPV. Only 2 out of 133 low- to intermediate-risk patients with CAC=0 had obstructive CAD. Budoff et al. demonstrated that an absence of CAC was highly associated with no obstructive CAD on angiography with 98% NPV and precludes the need for invasive angiography. The area under the receiver operating characteristic (ROC) curve for the discrimination of obstructive angiographic disease significantly increased when the combined model (CAC and risk factors) was compared with risk factors alone (ROC area: 0.830 ± 0.024 vs. 0.672 ± 0.019). (36)

Cardiogenic chest pain was strongly related to the presence of CAC, and coronary artery stenosis in patients without CAC is rare. (32,33) 20% to 50% of low-intermediate risk symptomatic patients were found to have a CAC score of zero.(34,35) In a systemic review of 18 studies, 10 037 symptomatic patients who underwent coronary CTA and CAC scanning revealed that 84% of patients with CAC=0 had no CAD, 13% had non-obstructive stenosis, 3.5% had ≥ 50% stenosis, and 1.4% had ≥ 70% stenosis on CCTA. The presence of CAC >0 had a pooled sensitivity of 98% for the detection of significant CAD on ICA. Zero CAC was associated with a relative risk ratio of 0.07 (95% CI, 0.03 to 0.19; P<0.00001) for ACS. Mouden et al.(36) in a study of 3501 patients with stable anginal symptoms and a low-intermediate PTP underwent SPECT myocardial perfusion imaging (MPI) and CAC scoring. 868 (mean age, 54 years ± 11; 70% female) patients were found to have calcium score of zero. 88% (n=766) patients had normal SPECT myocardial perfusion findings and 12% (n=102) patients were found to have abnormal SPECT or equivocal results. 91% of these 102 patients had normal coronaries and 9% (those with abnormal SPECT findings) had nonobstructive CAD on CCTA, excluding obstructive CAD in all of these patients. 9 patients (9%) were found to have normal

coronary arteries on ICA. In a median followup of 17-months, no patients had flow-limiting CAD (95% CI, 0-0.01). Previous studies reported a 3.1% of pooled incidence of obstructive CAD in patients without any CAC (374 out of 12,072)) using CCTA as a reference standard method (with a cutoff value of > 50% or > 70% luminal narrowing).(7,28,35,37–46) These compelling data in patients with CAC score of zero demonstrated the ability of CAC score in ruling out obstructive CAD in low-intermediate risk patients. Furthermore, McLaughlin et al.(47) and Laudon et al.(32) concluded that the low-moderate probability risk patients with calcium score of zero could be safely discharged and could potentially defer further diagnostic imaging.

Importance of CAC score of zero and its utility to predict the future cardiac events in symptomatic patients

The presence of any CAC (CAC >0) is a sensitive marker for obstructive CAD and might be the most appropriate screening threshold in patients presenting with the symptoms. A calcium score of zero in asymptomatic patients has been shown to predict an excellent 10-year survival rate of approximately 99 %.(48) The predictive value of CAC in diabetes(49), in younger adults(50) and in the elderly(51) has been confirmed. It is of major clinical importance if a similar relationship exists between a CAC score of 0 and ACS in symptomatic patients. However, a Bayesian approach to clinical decision making argued to consider pretest probability of obstructive CAD based on both the clinical presentation and risk factors along with a CAC score of 0 for accurate CAC interpretation.(52) A recent study of 3,468 patients who underwent anatomical testing were evaluated using 3 different prediction models based on the risk factors and calcium score. These models demonstrated moderate-good discrimination to estimate the PTP of CAD in patients with chronic stable angina and is significantly improved with addition of CAC data suggesting that the CAC score could add important information to the diagnostic work-up.(53)

For the past decade, the role of CAC in predicting the future coronary events in symptomatic patients have been demonstrated. In a multicenter retrospective study, Detarno et al.

(54) reviewed event data among 491 patients (mean age= 55 ± 12yrs; 57% males) who underwent CAC testing and coronary angiography. They found higher CAC were associated with an increased risk of coronary events over the next 30 months as compared to patients in the lowest quartile of score (OR=10.8, 95% CI, 1.4- 85.6) and only 1 (1/98=1.0%) event occurred in individuals with CAC=0. The atherosclerotic plaque burden was a considerable marker of disease but not stenosis severity. CAC was considered as a strong independent predictor of future events compared to sum of all conventional risk factors.(55)

The absence of CAC demonstrated a low pre-test probability for significant CAD among symptomatic patients at low to intermediate risk. Hoffmann et al. have reported only 1 event of ACS in the absence of calcified plaque among 368 (mean age 53±12 yrs; 61% male) low risk patients presenting to the ED(56) and these findings were consistent with Sarwar et al.(30) pooled analysis who reported that a positive CAC have a 99 % sensitivity and 99% NPV for the identification of ACS.

Studies have demonstrated that the absence of CAC is associated with a very low event rate in patients with chest pain syndrome. In a study of 192 patients with acute chest pain syndromes requiring hospitalization underwent CAC testing in ED and observed that absolute calcium scores were strongly related to the occurrence of hard events ($p< 0.001$) and all cardiovascular deaths ($p< 0.001$).(57) The frequency of events were significantly increased across ascending quartiles of CAC score and patients with CAC=0 have an 0.6% annualized event rate. Keelan et al. (58) reported significant event-free survival with CAC scores <100 relative to those with scores ≥100 (RR= 3.20; 95% CI,1.17 - 8.71; $p= 0.02$) among 288 patients over a mean followup of 6.9yrs. Only 1 in 87 patients with CAC < 20 experienced a subsequent hard event during follow-up. Schmermund et al. (32) demonstrated the relative risk (RR) estimate of MACE associated with a CAC score > 100 as 12.0 (95% CI, 4.7-30.6) and remained predictive in a multivariate analysis (RR=4.4; 95% CI, 1.5-12.6). Although these studies found the significant prognostic value for CAC, small sample size and small number of hard evets (<30)

limited the evidence of CAC utility in symptomatic patients as reflected in a class IIb guidelines recommendation for use.(36,59)

CAC=0 versus CAC >0 in stable symptomatic patients

Increasing CAC scores were significantly associated with increasing risk of major adverse cardiac events (MACEs), and zero scores were generally associated with low event. The pooled analysis of 7 studies reported the cumulative relative risk (RR) ratio for patients with a CAC score of zero as compared with patients with positive CAC scores was found to be 0.09.(30) Hou et al.(60) found the probability of 3-year MACE among 4,425 symptomatic patients referred for CCTA was only 2.1% for CACS = 0 (<1% per year) and 33.8% for CACS >400. The HR for patients with CACS of 101 to 400 and >400 compared with patients with CACS = 0 were 9.21 (95% CI: 6.50 to 13.05) and 22.22 (95% CI: 16.08 to 30.71), respectively. Budoff et al.(11) reported 9 hard events (cardiovascular death/ MI) occurred among 1457 negative CAC scans (CAC=0) with an event rate of 0.6%. This study investigators revealed that those with zero CAC (n-1457), only 0.5% had > 70% stenosis, 1.0% had 50% to 70% stenosis, 14.7% had nonobstructive stenosis and 80.8% had normal coronary arteries (zero stenosis) on CCTA. Furthermore, they noted very low event rate (1.4%) among the patients with CAC score of zero, 5.2 % with CAC score 100-400 and increasing to 6.4% in those with CAC scores> 400.

Wang e t al.(61) evaluated 1753 patients with stable chest pain who underwent CAC scoring ± CT coronary angiography (CTCA) as part of routine clinical care. 52.2% (n=915) patients (mean age 56.8 ± 12.0 years; 46.2% male) had a zero CAC score and 82.1% (n=751) of zero CAC patients underwent CCTA. On CCTA, 89.7% had normal coronary arteries, 8.4% had non-calcified CAD with < 50% stenosis and 1.9% had ≥ 50% stenosis in at least one coronary artery. The absolute annualized rates of MACEs in patients with CAC score of zero and any detectable CAC (CAC>0) were reported as 1.9 and 7.4 respectively (HR 3.8, p = 0.009) over a median follow-up of 2.2years.

In a recent study, Lo-Kioeng-Shioe et al.(62) included 19 studies including almost 35,000 patients to assess the pooled relative

risk (RR) ratios of CAC for MACE, and adjusted hazard ratios (HR) of the associations between different CAC strata (CAC 0–100,100–400, and ≥ 400, versus CAC $= 0$). 18 of 19 studies assessed the occurrence of cardiovascular events stratified per CAC status (CAC > 0 vs CAC $= 0$) and one study reported HRs per CAC stratum. A total 1601 (4.7%) cardiovascular events were analyzed and only 1.18% (n=158) of these events occurred in patients with a CAC score of zero. The pooled RR ratio was 5.71 (95%-CI: 3.98;8.19) in patients with CAC > 0 and for incidence of all-cause mortality or nonfatal myocardial infarction was 3.64 (95% CI: 2.68 to 4.96). The study investigators found both a threshold of CAC ≥ 100 and ≥ 400 yielded an increased cumulative relative risk for MACEs using a reference group of zero CAC score as shown in Table 2.

Additionally, the calcium score also guides therapy for primary prevention. In patients with atherosclerotic cardiovascular disease 10-year risk (ASCVD) of 5% or more with CAC > 0 should prompt initiation of statin therapy for primary prevention. Such practice can have greater impact in reducing future myocardial infarction risk, compared to discharging patients with a normal treadmill without a discussion of future cardiovascular risk and modulation through statin therapies.(63)

Table 2: Comparing risk for major adverse cardiac event at different thresholds of CAC*

Threshold of CAC score evaluated	No of studies	No of participants evaluated		RR (95% CI)	I^2	t^2
CAC score = 0 as reference group:						
Score > 0 vs 0	87(12–21,23–30)	30,057	Random effects	5.71 [3.98;8.19]	65%	0.2778
			Fixed effects	6.58 [5.58; 7.76]		
Score >/100 vs 0	7(13,18-21,24,28)	9434	Random effects	9.57 [6.87;13.33]	23%	0.0433
			Fixed effects	9.71 [7.70;12.25]		
Score >/400 vs 0	9(13,18-21,23-25,27)	8577	Random effects	8.30 [4.95;13.90]	77%	0.4083
			Fixed effects	9.21 [7.47;11.36]		
CAC score < 100 as reference group:						
Score >/100 vs <100	7(13,18-21,24,28)	13,198	Random effects	4.09 [2.85;5.89]	79%	0.1652
			Fixed effects	4.81 [4.19;5.53]		
Score >/400 vs <100	6(13,18-21,24)	10,762	Random effects	5.08 [3.52;7.34]	75%	0.1389
			Fixed effects	6.03 [5.16;7.05]		
CAC score < 400 as reference group:						
Score >/400 vs <400	9(13,18-21,23-25,27)	15,368	Random effects	3.30 [2.41;4.51]	83%	0.1746
			Fixed effects	3.83 [3.41;4.31]		

*Meta- analysis from 19 observational studies evaluated by Lo-Kioeng-Shioe et al.(62)

Conclusion:

The prompt and accurate evaluation of symptoms has immense implications for patient morbidity and mortality and health care economics. The primary goal of the evaluation of symptomatic patients is accurate risk stratification and identification or exclusion of ACS, rather than the detection of CAD. Determining the pre-test probability (PTP) of CAD based on the clinical presentation and history is helpful in the initial evaluation of symptomatic patients with suspected CAD which directly influences the decision for noninvasive diagnostic testing and treatment. The presence of atherosclerosis on CAC scan is a strong predictor of CAD than conventional risk factors, and this has been validated in multiple large epidemiologic and cohort studies. The CAC score is an effective filter in low -intermediate risk symptomatic patients; however, CACs cannot reliably exclude obstructive CAD. In patients with a CAC score of 0 the event rate is negligible and represents a population that will generally remain free of ASCVD for at least a decade. If CAC is present (CAC

score >0), additional imaging should be considered, dependent of the extent of coronary calcification and patient characteristics. It becomes clear that among patients with CAC = 0, a higher pretest probability of CAD is still predictive of significant coronary artery stenosis, emphasizing the utility of CAC = 0 in low-intermediate-risk patients. CAC has a great value when used in a binary fashion (CAC present or absent) in a selected patient population such as low-intermediate PTP of CAD. A finding of zero CAC might be used as a rationale to emphasize lifestyle therapies rather than pharmacotherapy and to forgo repeated imaging studies.

.

Bibliography

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation. 2020 Mar 3;141(9):e139–e596.
2. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. Circulation. 2007 Aug 14;116(7):e148–304.
3. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med. 1979 Jun 14;300(24):1350–1358.
4. Greenland P, Smith Jr SC, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people. Circulation. 2001 Oct 9;104(15):1863–1867.
5. Nasir K, Clouse M. Role of nonenhanced multidetector CT coronary artery calcium testing in asymptomatic and symptomatic individuals. Radiology. 2012 Sep;264(3):637–649.
6. Bhuiya FA, Pitts SR, McCaig LF. Emergency department visits for chest pain and abdominal pain: United States, 1999-2008. NCHS Data Brief. 2010 Sep;(43):1–8.
7. Cheng VY, Berman DS, Rozanski A, Dunning AM, Achenbach S, Al-Mallah M, et al. Performance of the traditional age, sex, and angina typicality-based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: results from the multinational coronary CT angiography evaluation for clinical outcomes: an international multicenter registry (CONFIRM). Circulation. 2011 Nov 29;124(22):, 1.
8. Chaitman BR, Bourassa MG, Davis K, Rogers WJ, Tyras DH, Berger R, et al. Angiographic prevalence of high-risk coronary artery disease in patient subsets (CASS). Circulation. 1981 Aug;64(2):360–367.
9. Pryor DB, Harrell FE, Lee KL, Califf RM, Rosati RA. Estimating the likelihood of significant coronary artery disease. Am J Med. 1983 Nov;75(5):771–780.
10. Reeh J, Therming CB, Heitmann M, Højberg S, Sørum C, Bech J, et al. Prediction of obstructive coronary artery disease and prognosis in

patients with suspected stable angina. Eur Heart J. 2019 May 7;40(18):1426–1435.
11. Budoff MJ, Mayrhofer T, Ferencik M, Bittner D, Lee KL, Lu MT, et al. Prognostic value of coronary artery calcium in the PROMISE study (prospective multicenter imaging study for evaluation of chest pain). Circulation. 2017 Nov 21;136(21):1993–2005.
12. McBride CB, Cheezum MK, Gore RS, Pathirana IN, Slim AM, Villines TC. Coronary artery calcium testing in symptomatic patients: an issue of diagnostic efficiency. Curr Cardiovasc Imaging Rep. 2013 Jun;6(3):211–220.
13. Zimetbaum PJ, Josephson ME. Use of the electrocardiogram in acute myocardial infarction. N Engl J Med. 2003 Mar 6;348(10):933–940.
14. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation. 2001 Oct 2;104(14):1694–1740.
15. Gianrossi R, Detrano R, Mulvihill D, Lehmann K, Dubach P, Colombo A, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. Circulation. 1989 Jul;80(1):87–98.
16. Lim SH, Sayre MR, Gibler WB. 2-D echocardiography prediction of adverse events in ED patients with chest pain. Am J Emerg Med. 2003 Mar;21(2):106–110.
17. Bedetti G, Pasanisi EM, Tintori G, Fonseca L, Tresoldi S, Minneci C, et al. Stress echo in chest pain unit: the SPEED trial. Int J Cardiol. 2005 Jul 20;102(3):461–467.
18. Chang SM, Nabi F, Xu J, Peterson LE, Achari A, Pratt CM, et al. The coronary artery calcium score and stress myocardial perfusion imaging provide independent and complementary prediction of cardiac risk. J Am Coll Cardiol. 2009 Nov 10;54(20):1872–1882.
19. Gallagher MJ, Ross MA, Raff GL, Goldstein JA, O'Neill WW, O'Neil B. The diagnostic accuracy of 64-slice computed tomography coronary angiography compared with stress nuclear imaging in emergency department low-risk chest pain patients. Ann Emerg Med. 2007 Feb;49(2):125–136.
20. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990 Mar 15;15(4):827–832.
21. Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. Ann Intern Med. 1999 May 4;130(9):719–728.
22. Lubbers M, Dedic A, Coenen A, Galema T, Akkerhuis J, Bruning T, et al. Calcium imaging and selective computed tomography angiography in comparison to functional testing for suspected coronary artery disease: the multicentre, randomized CRESCENT trial. Eur Heart J. 2016 Apr 14;37(15):1232–1243.

23. Smeeth L, Skinner JS, Ashcroft J, Hemingway H, Timmis A, Chest Pain Guideline Development Group. NICE clinical guideline: chest pain of recent onset. Br J Gen Pract. 2010 Aug;60(577):607–610.
24. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease - American College of Cardiology [Internet]. [cited 2020 Jun 3]. Available from: https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/03/07/16/00/2019-acc-aha-guideline-on-primary-prevention-gl-prevention
25. Recommendations | Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis | Guidance | NICE [Internet]. [cited 2020 Jun 9]. Available from: https://www.nice.org.uk/guidance/cg95/chapter/Recommendations#people-presenting-with-acute-chest-pain
26. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015 Apr 2;372(14):1291–1300.
27. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. Lancet. 2015 Jun 13;385(9985):2383–2391.
28. van Werkhoven JM, de Boer SM, Schuijf JD, Cademartiri F, Maffei E, Jukema JW, et al. Impact of clinical presentation and pretest likelihood on the relation between calcium score and computed tomographic coronary angiography. Am J Cardiol. 2010 Dec 15;106(12):1675–1679.
29. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol. 2007 Jan 23;49(3):378–402.
30. Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffmann U, Cury RC, et al. Diagnostic and prognostic value of absence of coronary artery calcification. JACC Cardiovasc Imaging. 2009 Jun;2(6):675–688.
31. Fernandez-Friera L, Garcia-Alvarez A, Bagheriannejad-Esfahani F, Malick W, Mirelis JG, Sawit ST, et al. Diagnostic value of coronary artery calcium scoring in low-intermediate risk patients evaluated in the emergency department for acute coronary syndrome. Am J Cardiol. 2011 Jan;107(1):17–23.
32. Laudon DA, Behrenbeck TR, Wood CM, Bailey KR, Callahan CM, Breen JF, et al. Computed tomographic coronary artery calcium assessment for

evaluating chest pain in the emergency department: long-term outcome of a prospective blind study. Mayo Clin Proc. 2010 Apr;85(4):314–322.
33. Ho JS, Fitzgerald SJ, Stolfus LL, Wade WA, Reinhardt DB, Barlow CE, et al. Relation of a coronary artery calcium score higher than 400 to coronary stenoses detected using multidetector computed tomography and to traditional cardiovascular risk factors. Am J Cardiol. 2008 May 15;101(10):1444–1447.
34. Rijlaarsdam-Hermsen D, Kuijpers D, van Dijkman PRM. Diagnostic and prognostic value of absence of coronary artery calcification in patients with stable chest symptoms. Neth Heart J. 2011 May;19(5):223–228.
35. Villines TC, Hulten EA, Shaw LJ, Goyal M, Dunning A, Achenbach S, et al. Prevalence and severity of coronary artery disease and adverse events among symptomatic patients with coronary artery calcification scores of zero undergoing coronary computed tomography angiography: results from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry. J Am Coll Cardiol. 2011 Dec 6;58(24):2533–2540.
36. Mouden M, Timmer JR, Reiffers S, Oostdijk AHJ, Knollema S, Ottervanger JP, et al. Coronary artery calcium scoring to exclude flow-limiting coronary artery disease in symptomatic stable patients at low or intermediate risk. Radiology. 2013 Oct;269(1):77–83.
37. Kelly JL, Thickman D, Abramson SD, Chen PR, Smazal SF, Fleishman MJ, et al. Coronary CT angiography findings in patients without coronary calcification. AJR Am J Roentgenol. 2008 Jul;191(1):50–55.
38. Morita H, Fujimoto S, Kondo T, Arai T, Sekine T, Matsutani H, et al. Prevalence of computed tomographic angiography-verified high-risk plaques and significant luminal stenosis in patients with zero coronary calcium score. Int J Cardiol. 2012 Jul 12;158(2):272–278.
39. de Carvalho MSL, de Araújo Gonçalves P, Garcia-Garcia HM, de Sousa PJ, Dores H, Ferreira A, et al. Prevalence and predictors of coronary artery disease in patients with a calcium score of zero. Int J Cardiovasc Imaging. 2013 Dec;29(8):1839–1846.
40. Sosnowski M, Pysz P, Szymański L, Gola A, Tendera M. Negative calcium score and the presence of obstructive coronary lesions in patients with intermediate CAD probability. Int J Cardiol. 2011 Apr 1;148(1):e16–8.
41. Ergün E, Koşar P, Oztürk C, Başbay E, Koç F, Koşar U. Prevalence and extent of coronary artery disease determined by 64-slice CTA in patients with zero coronary calcium score. Int J Cardiovasc Imaging. 2011 Mar;27(3):451–458.
42. Alqarqaz M, Zaidan M, Al-Mallah MH. Prevalence and predictors of atherosclerosis in symptomatic patients with zero calcium score. Acad Radiol. 2011 Nov;18(11):1437–1441.
43. Kim YJ, Hur J, Lee H-J, Chang H-J, Nam JE, Hong YJ, et al. Meaning of zero coronary calcium score in symptomatic patients referred for coronary computed tomographic angiography. Eur Heart J Cardiovasc Imaging. 2012 Sep;13(9):776–785.

44. Nieman K, Galema TW, Neefjes LA, Weustink AC, Musters P, Moelker AD, et al. Comparison of the value of coronary calcium detection to computed tomographic angiography and exercise testing in patients with chest pain. Am J Cardiol. 2009 Dec 1;104(11):1499–1504.
45. Büyükterzi M, Türkvatan A, Büyükterzi Z. Frequency and extent of coronary atherosclerotic plaques in patients with a coronary artery calcium score of zero: assessment with CT angiography. Diagn Interv Radiol. 2013 Apr;19(2):111–118.
46. Uretsky S, Rozanski A, Singh P, Supariwala A, Atluri P, Bangalore S, et al. The presence, characterization and prognosis of coronary plaques among patients with zero coronary calcium scores. Int J Cardiovasc Imaging. 2011 Jul;27(6):805–812.
47. McLaughlin VV, Balogh T, Rich S. Utility of electron beam computed tomography to stratify patients presenting to the emergency room with chest pain. Am J Cardiol. 1999 Aug 1;84(3):327–8, A8.
48. Blaha M, Budoff MJ, Shaw LJ, Khosa F, Rumberger JA, Berman D, et al. Absence of coronary artery calcification and all-cause mortality. JACC Cardiovasc Imaging. 2009 Jun;2(6):692–700.
49. Malik S, Zhao Y, Budoff M, Nasir K, Blumenthal RS, Bertoni AG, et al. Coronary Artery Calcium Score for Long-term Risk Classification in Individuals With Type 2 Diabetes and Metabolic Syndrome From the Multi-Ethnic Study of Atherosclerosis. JAMA Cardiol. 2017 Dec 1;2(12):1332–1340.
50. Yano Y, O'Donnell CJ, Kuller L, Kavousi M, Erbel R, Ning H, et al. Association of Coronary Artery Calcium Score vs Age With Cardiovascular Risk in Older Adults: An Analysis of Pooled Population-Based Studies. JAMA Cardiol. 2017 Sep 1;2(9):986–994.
51. Carr JJ, Jacobs DR, Terry JG, Shay CM, Sidney S, Liu K, et al. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. JAMA Cardiol. 2017 Apr 1;2(4):391–399.
52. Blaha MJ, Blumenthal RS, Budoff MJ, Nasir K. Understanding the utility of zero coronary calcium as a prognostic test: a Bayesian approach. Circ Cardiovasc Qual Outcomes. 2011 Mar;4(2):253–256.
53. Genders TSS, Coles A, Hoffmann U, Patel MR, Mark DB, Lee KL, et al. The external validity of prediction models for the diagnosis of obstructive coronary artery disease in patients with stable chest pain: insights from the PROMISE trial. JACC Cardiovasc Imaging. 2018;11(3):437–446.
54. Detrano R, Hsiai T, Wang S, Puentes G, Fallavollita J, Shields P, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. J Am Coll Cardiol. 1996 Feb;27(2):285–290.
55. Kennedy J, Shavelle R, Wang S, Budoff M, Detrano RC. Coronary calcium and standard risk factors in symptomatic patients referred for coronary angiography. Am Heart J. 1998 Apr;135(4):696–702.

56. Hoffmann U, Bamberg F, Chae CU, Nichols JH, Rogers IS, Seneviratne SK, et al. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. J Am Coll Cardiol. 2009 May 5;53(18):1642–1650.
57. Georgiou D, Budoff MJ, Kaufer E, Kennedy JM, Lu B, Brundage BH. Screening patients with chest pain in the emergency department using electron beam tomography: a follow-up study. J Am Coll Cardiol. 2001 Jul;38(1):105–110.
58. Keelan PC, Bielak LF, Ashai K, Jamjoum LS, Denktas AE, Rumberger JA, et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. Circulation. 2001 Jul 24;104(4):412–417.
59. Lauer MS, Topol EJ. Clinical trials--multiple treatments, multiple end points, and multiple lessons. JAMA. 2003 May 21;289(19):2575–2577.
60. Hou Z, Lu B, Gao Y, Jiang S, Wang Y, Li W, et al. Prognostic value of coronary CT angiography and calcium score for major adverse cardiac events in outpatients. JACC Cardiovasc Imaging. 2012 Oct;5(10):990–999.
61. Wang X, Le EPV, Rajani NK, Hudson-Peacock NJ, Pavey H, Tarkin JM, et al. A zero coronary artery calcium score in patients with stable chest pain is associated with a good prognosis, despite risk of non-calcified plaques. Open Heart. 2019 Apr 11;6(1):e000945.
62. Lo-Kioeng-Shioe MS, Vavere AL, Arbab-Zadeh A, Schuijf JD, Rochitte CE, Chen MY, et al. Coronary calcium characteristics as predictors of major adverse cardiac events in symptomatic patients: insights from the CORE 320 multinational study. J Am Heart Assoc. 2019 Mar 19;8(6):e007201.
63. Shekar C, Budoff M. Calcification of the heart: mechanisms and therapeutic avenues. Expert Rev Cardiovasc Ther. 2018 Jul;16(7):527–536.