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Authors

Sheppard, John P
Lakshmanan, Suvasini
Lichtenstein, Seth J
et al.

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Age and the power of zero CAC in cardiac risk assessment: overview of the literature and a cautionary case

John P Sheppard, Suvasini Lakshmanan, Seth J Lichtenstein, Matthew J Budoff, Sion K Roy

Authors

John P Sheppard
Resident Physician

Department of Internal Medicine, Yale New Haven Hospital, 20 York Street, New Haven, Connecticut, 06510, USA

Suvasini Lakshmanan
Physician Fellow

Division of Cardiovascular Medicine, University of Iowa Hospitals & Clinics, 200 Hawkins Drive, Iowa City, Iowa, 52242, USA

Seth J Lichtenstein
Physician Fellow

Matthew J Budoff
Professor of Medicine, David Geffen School of Medicine at UCLA, Investigator, Lundquist Institute, and Program Director and Director of Cardiac CT

Sion K Roy
Associate Program Director and Director of Inpatient Cardiac CT

Harbor-UCLA Medical Center, 1000 West Carson Street, Torrance, California, 90502, USA

Correspondence to:
Professor M J Budoff, Lundquist Institute, 1124 West Carson Street, Torrance, CA 90502, USA
(mbudoff@labiomed.org)

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The coronary artery calcium (CAC) score is a marker of advanced coronary atherosclerosis. Numerous prospective cohorts have validated CAC as an independent marker that improves prognostication in atherosclerotic cardiovascular disease (ASCVD) beyond traditional risk factors. Accordingly, CAC is now incorporated into international cardiovascular guidelines as a tool to inform medical decision-making. Particular interest concerns the significance of zero CAC score (CAC=0). While many studies report CAC=0 to virtually exclude obstructive coronary artery disease (CAD), non-negligible rates of obstructive CAD despite CAC=0 are reported in certain populations. Overall, the current literature supports the power of zero CAC as a strong downward risk classifier in older patients, whose CAD burden predominantly involves calcified plaque. However, with their higher burden of non-calcified plaque, CAC=0 does not reliably exclude obstructive CAD in patients under 40 years. Illustrating this point, we present a cautionary case of a 31-year-old patient found to have severe two-vessel CAD despite CAC=0. We highlight the value of coronary computed tomography angiography (CCTA) as the gold-standard non-invasive imaging modality when the diagnosis of obstructive CAD is in question.

Introduction

Since its inception by Agatston and Janowitz in 1990, coronary artery calcium (CAC) scoring has blossomed from a novel imaging tool to an internationally accepted biomarker of cardiovascular risk included in current preventive atherosclerotic cardiovascular disease (ASCVD) guidelines.[1-7] With its growing adoption, debate has emerged over the proper use of CAC scores in risk stratification, with controversy surrounding its role in excluding obstructive disease in symptomatic patients. Presently, we focus on the role of CAC in risk stratification for coronary heart disease (CHD). We review the overwhelming evidence validating CAC as a diagnostic and prognostic indicator in older adults but highlight its unreliability in younger patients under 40 years. We conclude with a cautionary case of a 31-year-old man admitted to our hospital who was found to have severe two-vessel coronary artery disease (CAD) despite zero CAC score.

Clinical overview

CAC as a CHD risk marker: the view from clinical end point studies

A nascent field of clinical imaging research investigating CAC grew throughout the 1990s,[8] and culminated in the publication of foundational end point studies over the subsequent decade, establishing CAC's utility as a marker of CHD (**table 1**).[1,2,9-14] This work established, not only a proportional relationship between CAC score and incident CHD risk, but demonstrated CAC's ability to improve CHD prediction independent of traditional risk factors, such as those included in the Framingham risk score (FRS).[15] Greenland *et al.* found a 3–9% increase in 10-year coronary event risk beyond FRS criteria in individuals with

Table 1. Notable studies establishing coronary artery calcium (CAC) as a biomarker in atherosclerotic cardiovascular disease (ASCVD) risk assessment

Study	Year	Country	Patients	Population	Age, years	Follow-up, years	Key findings
Rotterdam[10]	2005	Netherlands	1,795	Asymptomatic adults	71 (62–85)	3.3 ± 0.8	Adding CAC score to FRS improved CHD risk prediction
Prospective Army Coronary Calcium (PACC) Project[9]	2005	USA	2,000	Asymptomatic active-duty military	42.9 ± 2.8 (40–50)	3.0 ± 1.6 (1–6)	Hazard ratio increase of 4.3 for incident CAD per CAC tertile. CAC>0 in men associated with relative risk of 12 for incident CAD
Cooper Clinic Cohort[11]	2005	USA	10,746	Asymptomatic adults	53.8 ± 9.9 (22–96)	3.5 ± 1.4	Dose-dependent relationship between CAC score and incident CHD surviving adjustment for traditional risk factors. CAC associated with CHD in both younger (<40) and older (>65) patients
St. Francis Heart Study[12]	2005	USA	4,903	Asymptomatic adults	59 ± 6	4.3	CAC predicted incident CAD better than FRS
MESA[13]	2008	USA	6,722	Asymptomatic multi-ethnic adults	62.2 ± 10.2 (45–84)	3.8	Doubling of CAC score associated with 15–35% increased risk of major coronary event and 14% relative increase in incident ASCVD
Heinz Nixdorf Recall Study[19]	2010	Germany	4,129	Asymptomatic adults without known CAD	59 ± 8 (45–75)	5.1 ± 0.3	Reclassifying intermediate risk patients based on FRS to low risk (if CAC<100) or high risk (if CAC≥400) categories improved prediction of incident coronary events
Dallas Heart Study[69]	2015	USA	2,084	Multi-ethnic adults without diabetes or CVD	44.4 ± 9.0	9.2 ± 1.3	CAC score improved CHD risk classification in younger adults
BioImage[63]	2016	USA	5,805	Adults without known CVD	68.9 ± 6.0	2.7	CAC-guided reclassification of CHD risk achieved a 22% improvement in specificity with no loss in sensitivity, driven by down-classifying risk among patients with CAC=0
Jackson Heart Study[70]	2016	USA	2,944	African-American adults	60 (21–64)	–	Adding CAC score to FRS improved prediction of CVD prevalence
Framingham Offspring[16]	2016	USA	3,486	Men ≥35 y, Women ≥40 y	50 ± 10	8	CAC improved prediction of incident CHD beyond traditional risk factors and accurately reclassified 2/3 of intermediate-risk patients
CARDIA[71]	2017	USA	5,115	Black and White younger adults	40.3 ± 3.6 (at study year 15)	12.5	CAC>0 associated with 5-fold increase in CHD incidence after adjustment for baseline risk. CVD risk factors in early adult life identified patients who later developed CAC
CAC Consortium[72]	2020	USA	66,636	Adults without known CHD	54 ± 11	12.5	CAC associated with CHD-attributable, CVD-attributable and all-cause mortality in a dose-dependent manner

Key: ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CAD = coronary artery disease; CHD = coronary heart disease; CVD = cardiovascular disease; FRS = Framingham risk score

CAC score over 300.[14] The Rotterdam study found CAC scores improved prediction of incident CHD, ASCVD, and all-cause mortality beyond traditional risk factors among 1,795 asymptomatic adults over 70 years.[10] The multi-ethnic study of atherosclerosis (MESA) extended these findings to a diverse cohort including Black (28%), Hispanic (22%), Chinese (12%), and White (39%) patients.[13] MESA found an 18–39% increase in coronary event risk associated with each doubling of the CAC score, without major differences between ethnic groups.[13] The Framingham Offspring study further validated these observations among 3,486 descendants of the original Framingham Heart Study.[16] Again, CAC improved CHD prediction beyond Framingham risk factors, and correctly reclassified 85% of patients initially deemed at intermediate risk for CHD.[16] Notable cohort studies establishing the value of CAC in ASCVD risk assessment are summarised in **table 1**.

CAC and the 'power of zero'

CAC's prognostic power to improve cardiovascular risk classification had major implications. Among end point studies, excellent cardiovascular outcomes were noted among patient subgroups with zero detectable CAC (CAC=0). Composite analysis of 16,106 asymptomatic patients with CAC=0 spanning 13 early observational studies found an annual coronary event rate of 0.027%, translating to a negative predictive value (NPV) of 98.1% over a mean follow-up of 4.7 years.[17] Other major studies reported annual event rates as low as 0.06–0.16% in asymptomatic adults without detectable CAC.[9,12,18-20] Initial results from the CAC Consortium cohort

found yearly all-cause mortality of 0.87% among 19,898 asymptomatic middle-age adults with CAC=0,[21] and risk of all-cause mortality doubled in patients with even the lowest levels of detectable calcium (i.e. CAC score of 1–10). At 12-year follow-up, incident CHD-attributable mortality among patients with CAC=0 was only 0.17%.[22] Subsequent analysis of the MESA cohort found CAC=0 to be the greatest downward indicator of 10-year CHD and overall ASCVD risk among 13 other laboratory, imaging, and clinical risk markers.[23]

The profound differences observed in cardiovascular events among patients at either CAC score extreme allow for more accurate reclassification of ASCVD risk. This approach has been validated in numerous studies and is of relevance for patients estimated to be at intermediate, borderline, or even low ASCVD risk based on the pooled cohort equations (PCE).[5] For instance, among 2,966 MESA patients who were eligible for statin therapy per the contemporary US cholesterol guidelines, 44% had zero detectable CAC.[24,25] Among this subset, the observed 10-year ASCVD event rate was only 4.2 per 1,000 person-years, and CAC=0 reclassified 49% of statin-eligible patients to a 10-year ASCVD risk <5%, below the suggested risk threshold for statin therapy.[24] Valenti *et al.* even proposed a 15-year 'warranty period' among asymptomatic adults with CAC=0 who were already at low or intermediate risk by PCE, noting a survival rate of 95.1% after mean follow-up of 14.6 years.[26] Ultimately, this prognostic power has led to CAC's inclusion in the current European guidelines as a cardiovascular risk modifier for asymptomatic patients.[27] CAC scoring is also incorporated in the current US cholesterol guidelines as a class IIa recommendation to inform decision-making regarding statin therapy in adults over 40 years at borderline risk,[4] although debate remains as to CAC's role in de-escalating pharmacotherapy.[28]

CT-based screening for obstructive CAD in the symptomatic patient

While much effort has focused on CAC's use in asymptomatic populations from a preventive health standpoint, its diagnostic applications in patients with chest pain has also garnered considerable interest. Safe and cost-effective risk stratification of chest pain presents a major challenge in both the ambulatory and emergency setting. Chest pain accounts for over six million emergency room visits in the US annually, with three million patients ultimately discharged with non-cardiac diagnoses.[29]

Excluding obstructive CAD is of cardinal interest in any patient with chest pain, and particularly in those whose presentation raises suspicion for acute coronary syndrome (ACS). From a non-invasive imaging standpoint, coronary computed tomography angiography (CCTA) is unrivaled in the diagnosis of CAD and grading of coronary luminal stenosis. The ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial reported sensitivity of 94–95% and NPV of 99% for excluding moderate (≥50%) or severe (≥70%) coronary stenosis with CCTA compared with angiography.[30] Subsequent studies consistently demonstrated >90% sensitivity and superior performance with CCTA compared with myocardial perfusion imaging for detecting obstructive CAD.[31,32]

Increasingly, CCTA has been adopted by emergency departments (EDs) in the US to facilitate decision-making in patients undergoing ACS rule-out and, potentially, defer formal angiography. In the ROMICAT-II (Rule Out Myocardial Ischemia/Infarction Using Computer Assisted Tomography) trial, 1,000 patients presenting to the ED with acute chest pain and suspicion for ACS despite negative cardiac enzymes and lack of electrocardiogram (ECG) changes were randomised to undergo early CCTA or standard evaluation.[33] Patients who underwent early CCTA benefited from shorter length of stay and higher rates of direct ED discharge, and no cases of ACS went undetected (i.e. no re-presentations at 72 hours post-discharge with subsequent positive work-up).

CCTA's role as a screening tool for chest pain syndrome is also well-validated in the outpatient setting. The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial randomised patients with stable chest pain and intermediate pre-test probability to undergo either CCTA or functional testing.[34] Incidence of the primary end point (death, myocardial infarction, or hospitalisation for unstable angina) at follow-up was lower in patients who underwent CCTA (0.9%) versus functional testing (2.1%), despite lower prevalence of normal test results in the CCTA arm (33% *vs.* 78%). CCTA had superior discriminative ability in event prediction (c-statistic 0.72 *vs.* 0.64) and higher diagnostic yield compared with functional testing.[35] Of note, the SCOT-HEART (Scottish COmputed Tomography of the HEART) trial randomised 4,146 outpatients with stable chest pain to either standard care or standard care plus early CCTA.[36] Patients undergoing early CCTA had lower incidence of the composite end point of non-fatal myocardial infarction (MI) or CHD-attributable mortality at five-year follow-up. In terms of resource utilisation, there was no difference in five-year rates of angiography or revascularisation procedures, but patients referred to CCTA were more likely to be initiated on preventive or anti-anginal therapies.[36]

Many large-scale studies have examined the reliability of CAC in patients with chest pain, and have yielded favourable results. Meta-analysis across 32,477 symptomatic patients found that presence of CAC (CAC>0) was strongly associated with cardiovascular event risk, with pooled risk ratios (RR) of 6.1 for incident ASCVD and 7.9 for all-cause mortality.[37] **Table 2** lists several well-powered cohort studies evaluating the reliability of CAC=0; many data are derived from studies of symptomatic patients undergoing both CAC scoring and CCTA.[38] The CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry) study examined 10,037 symptomatic patients without known CAD who underwent both CAC scoring and CCTA, and found that CAC=0 excluded obstructive CAD with NPV of 96.5% for ≥50% stenosis and 98.6% for ≥70% stenosis.[39] The PROMISE trial also included 4,209 patients who underwent CCTA and CAC scoring.[34] Among 1,457 patients with CAC=0, only 22 patients (1.5%) had ≥50% stenosis and only seven (0.5%) had ≥70% stenosis on CCTA, corresponding to NPV of 98.5% and 99.5%, respectively.[34]

Table 2. Notable CAC=0 studies*

Study	Year	Country	Patients	Population	Age, years	Follow-up, years	Confirmatory imaging modality	Findings in CAC=0 patients
Knez[68]	2004	Germany	2,115	Symptomatic adults	62 ± 19	–	ICA	NPV of 100% (≥50% stenosis)
Rubinshtein[54]	2007	Israel	668	Symptomatic adults	54 ± 12	–	CCTA	NPV of 93% (≥50% stenosis)
CONFIRM[39]	2011	International	10,037	Symptomatic adults	57 ± 12	2.1	CCTA	NPV of 96.5% (≥50% stenosis), 98.6% (≥70% stenosis)
Chang[58]	2011	USA	1,049	Acute chest pain, suspected ACS	48.1	30 days	CCTA	NPV of 77.6% (>50% stenosis). 4/17 patients with CAC=0 and obstructive CAD had AMI. Age <50 70% more likely to have obstructive CAD with CAC=0
Kim[73]	2012	Korea	2,088	Symptomatic adults	58 ± 10	2.8	CCTA	NPV of 95.7% (≥50% stenosis)
Hulten[74]	2014	USA	1,145	Symptomatic adults	55 ± 12	2.4	CCTA	NPV of 99% (≥50% stenosis), 99.6% (≥70% stenosis)
Valenti[26]	2015	USA	9,715	Asymptomatic adults	53.4 ± 10.5	14.6	–	15-year warranty period against mortality in individuals at low-to-intermediate risk regardless of age or sex
PROMISE[34]	2017	North America	4,209	Symptomatic adults at intermediate risk	60.6 ± 8.2	2.2	CCTA	NPV of 98.5% (≥50% stenosis), 99.5% (≥70% stenosis)
Mittal[48]	2017	UK	2,730	Symptomatic adults	56.9 ± 12.4	5.2	CCTA	NPV of 99.5% (≥70% stenosis)
Walter Reed[75]	2018	USA	13,644	Active-duty military, no prior CVD	50 ± 8	9.4	–	NNT of 3,571 to prevent MACE with 10 years of statin therapy (NNT=12 for CAC>100)
Wang[43]	2019	UK	1,753	Symptomatic adults, suspected stable CAD	56.8 ± 12.0	2.2	CCTA	NPV of 98.1% (≥50% stenosis)
Mortensen[60]	2022	Denmark	23,759	Symptomatic adults	58	4.3	CCTA	CAC=0 prevalence of 93% (age <40) *vs.* 5% (age >70). Likelihood ratio of ≥50% stenosis given CAC=0 of 0.68 (age <40) *vs.* 0.18 (age >70)

*Expanded from Gagel *et al.*[2] Included studies are limited to cohorts including ≥500 patients.

Key: ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAC = coronary artery calcium; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CVD = cardiovascular disease; ICA = invasive coronary angiography; MACE = major adverse cardiovascular event; NNT = number needed to treat; NPV = negative predictive value

The CRESCENT (Calcium Imaging and Selective CT Angiography in Comparison to Functional Testing for Suspected Coronary Artery Disease) trial evaluated a tiered approach to anatomic testing among 350 patients with stable CAD.[40] Patients randomised to the anatomic testing arm first underwent CAC scoring and proceeded to CCTA only if estimated pre-test probability for obstructive CAD was >70%, or if CAC was present on computed tomography (CT). Among 242 patients randomised to anatomic testing, 98 patients had CAC=0 and none sustained major adverse cardiovascular events (MACE) or required further testing after one year of follow-up.[40] The tiered anatomic testing approach was associated with reduced need for further diagnostic testing, lower cumulative testing costs, and shorter time to final diagnosis relative to a functional testing-based strategy.[38,40] Similar results were obtained in the CRESCENT-II trial, with zero of 45 patients with CAC=0 suffering MACE or subsequently diagnosed with obstructive disease at follow-up.[38,41] Low rates of obstructive CAD among patients with CAC=0 were also found in *post-hoc* analysis of the SCOT-HEART trial,[38,42] with only around 1% MACE incidence after five years of follow-up.[42] Wang *et al.* reported outcomes in a prospective series of 1,753 symptomatic patients with stable CAD.[43] CAC=0 achieved a NPV of 98.1% for excluding ≥50% stenosis on CCTA. At two-year follow-up, MACE incidence was only 0.6% (five patients) among 751 patients with CAC=0.[43] Sixty-three patients (8.4%) with CAC=0 had subclinical non-calcified plaque on CCTA, but there was zero MACE incidence among this subgroup.[43]

A subset of studies focused specifically on the reliability of CAC for excluding ACS in the emergency setting. Early case series pointed to the promise of CAC=0, reporting sensitivity of 97–100% for excluding ACS in patients with chest pain.[44-46] Bittner *et al.* reviewed 826 consecutive patients presenting to the ED with acute chest pain.[38,47] Among 444 patients with CAC=0, rates of obstructive CAD were very low, with NPV of 99.5% for ≥50% stenosis and 99.8% for ≥70% stenosis;[47] however, the exclusion of patients with positive initial cardiac enzymes reduced pre-test probability with an overall ACS rate of only 7.9%.[47] Mittal *et al.* evaluated incidence of obstructive CAD in an observational ED cohort including 2,730 patients undergoing

CCTA.[48] Among the 52.5% of patients with CAC=0, NPV of 98.3% and 99.5% were achieved for excluding ≥50% or ≥70% stenosis, respectively.[48] All 24 patients with ≥50% stenosis on CCTA underwent formal angiography, with flow-limiting stenoses ultimately found in only four patients. Patients with CAC=0 had an annual all-cause mortality of only 0.3%, with zero reported coronary events across over five years of mean follow-up.[38,48] Furthermore, the presence of non-calcified plaque on subsequent imaging had no association with mortality among patients with CAC=0.[48]

While the accuracy of CAC score in predicting obstructive CAD is generally excellent, some studies have reported less favourable results. As noted in the CONFIRM study,[39] other early reported rates of obstructive CAD were as high as 7–38% in patients with CAC=0, although these data originated from small retrospective case series.[49-54] Even the CONFIRM authors concluded that CAC=0 did not reliably exclude CAD in their symptomatic cohort, given that 3.5% of this subgroup still had ≥50% stenosis on CCTA.[39] A meta-analysis by Sarwar *et al.* found CAC=0 excluded obstructive disease (>50% stenosis) with pooled sensitivity of 98% and NPV of 93% across 18 studies of symptomatic patients undergoing CAC scoring and invasive angiography.[55] While promising, such error rates preclude deferring CCTA if reasonable suspicion exists for underlying obstructive disease.

Value of CAC=0 across the lifespan

Discrepant results in the literature raise the question of whether zero CAC score is equally meaningful in all patients. The use of CAC=0 to down-classify obstructive CAD risk is debated, especially in younger symptomatic patients with pre-test risk factors for disease. Evidence increasingly points to age as a critical factor in interpreting CAC score. The biological rationale is intuitive: atherosclerosis progresses over decades,[56,57] with intimal calcification occurring late in its course.[58,59] Older adults with CAD have accumulated calcified plaque over many decades of life, explaining higher average CAC scores and higher prevalence of detectable CAC relative to younger patients.[60] As CAC specifically detects calcified plaque, it is unsurprising that CAC=0 excludes clinical disease more accurately in older patients.

Relative to older patients, most coronary plaque in younger patients with CAD is non-calcified.[61] This is supported by MESA and related studies that demonstrate the subsequent appearance and progression of CAC over years on serial CT, in a manner correlating with cardiovascular risk factors, in patients with CAC=0 on their baseline scan.[62] As a fraction of total coronary plaque, non-calcified plaque is more prevalent in younger populations,[63] particularly in patients presenting with ACS in the absence of stable CAD.[64] Specific cardiovascular risk factors, including diabetes and hyperlipidaemia, are also linked with higher burden of non-calcified plaque and are critical to consider in younger patients.[61,65,66]

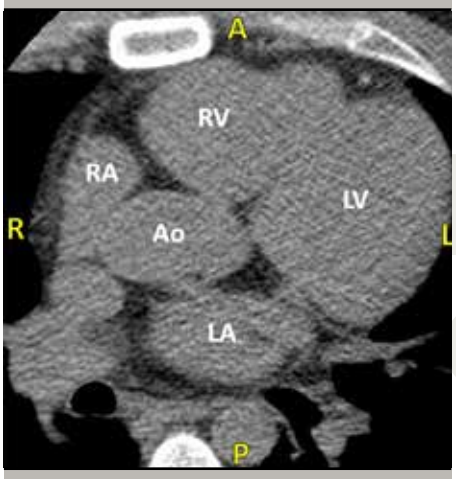
The importance of age in CAC score interpretation is supported by literature findings.[67] An early prospective study by Knez *et al.* evaluated 2,115 symptomatic patients with chest pain referred for formal angiography (mean age 62 years). Among 326 patients with CAC=0, none had significant CAD defined as ≥50% luminal stenosis.[68] Among 1,247 patients with any degree of angiographically confirmed stenosis, only eight had CAC=0 (0.6%), seven of whom were under age 45 years.[68] While the rate of subclinical stenosis in symptomatic adults over age 45 years with CAC=0 was only ~0.05%, the rate in adults under 45 years was ~2-5%, up to 100-fold higher.[68] In another notable study, Chang *et al.* reported a prospective series of 1,049 patients (median age 48 years) presenting to an ED with acute chest pain and suspicion for ACS. Obstructive CAD was found in 17 of 76 patients with CAC=0 (NPV=77.6%), four of whom suffered a cardiovascular event within 30 days.[58] The authors found that patients under 50 years were 70% more likely to have obstructive CAD with CAC=0.[58] Cademartiri and colleagues reported ≥50% stenosis in 14.6% of 279 patients selected on the basis of suspected CAD, despite CAC=0.[49] Although these numbers were driven by high pre-test probability in terms of symptoms and risk profile (including known ischaemic changes on stress testing in many patients), it bears mention that mean age across this cohort was only 48 years. Akram *et al.* also published a series of 210 patients referred for CAC scoring and CCTA, and reported >70% stenosis in four of 49 (8.2%) symptomatic patients on CCTA, despite CAC=0; three of these four patients were under age 45 years.[50]

Recently, the age-dependent relationship between CAC scores and risk of obstructive CAD has been rigorously examined in a well-conducted study by Mortensen *et al.*[60] Mortensen and colleagues examined data from 23,759 patients aged 18 years or older from the Western Denmark Heart Registry. Among 13,496 patients with CAC=0 (57%), 725 patients (5.7%) had obstructive CAD on CCTA, corresponding to an NPV of 94.3%. Prevalence of CAC=0, however, varied markedly with age. CAC=0 was observed in 93% (1,278 of 1,372) of patients under 40 years, compared with only 51% (11,493 of 22,387) of patients over 40 years. Younger patients with obstructive CAD were much more likely to have non-calcified plaque. Among patients with obstructive CAD, CAC=0 was observed in 58% (39/68) of patients <40 years compared with only 14% (686/4,975) of patients >40 years, and 5% (52/964) of patients >70 years. Moreover, the diagnostic value of CAC=0 in reclassifying obstructive CAD risk increased steadily with age. After adjusting for age, sex, smoking, diabetes, and symptom characteristics, the risk-adjusted diagnostic likelihood ratio of obstructive CAD for CAC=0 ranged from 0.68 (32% lower CAD likelihood) in patients aged 18–39 years down to 0.18 (82% lower CAD likelihood) for patients >70 years. These findings corroborate the existing literature and demonstrate the age-dependent value of a zero CAC score.

Illustrative case

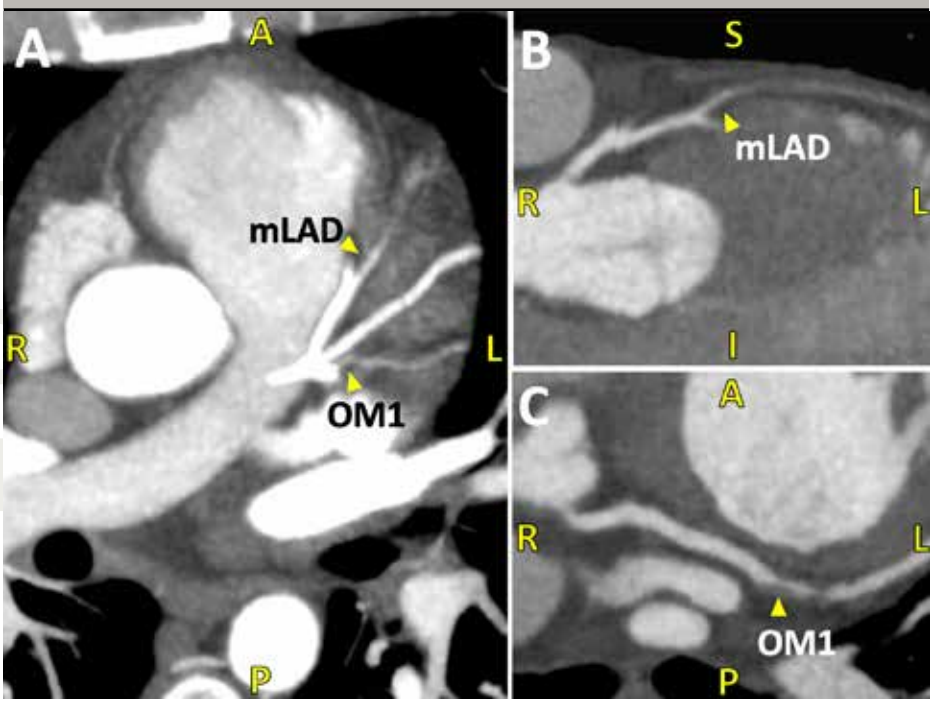
A 31-year-old man presented to our hospital with intermittent left-sided chest pain and radiation to his left arm. Associated symptoms included shortness of breath and diaphoresis. He described experiencing similar symptoms in recent months. Medical history was pertinent for obesity, uncontrolled diabetes, and hypertension. Laboratory values revealed a glycosylated haemoglobin (HbA_{1c}) of 14.1% and lipid profile significant for total cholesterol of 364 mg/dL, high-density lipoprotein (HDL)

Figure 1. Axial cardiac computed tomography (CT) image demonstrating zero detectable calcium burden



Key: Ao = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle

Figure 2. A. Axial CT angiography image demonstrating occlusions of the mid-left anterior descending (mLAD) and first obtuse marginal (OM1). B. Mid-LAD total occlusion in coronal view. C. OM1 occlusion in axial view



24 mg/dL, and triglycerides of 1,146 mg/dL. ECG showed normal sinus rhythm without evidence of ischaemia, infarction, or hypertrophy. Echocardiogram was structurally normal, with normal ejection fraction and wall motion. Troponin I levels were intermediate (peak 0.24 ng/mL) and he was assessed as having intermediate-risk chest pain.

As part of a protocol at our hospital, patients with chest pain and an intermediate risk profile proceed directly to CCTA to exclude obstruction. The patient had a CAC score of zero (**figure 1**), but CCTA revealed severe two-vessel disease with total occlusion of the mid-left anterior descending (LAD) and proximal first obtuse marginal (OM1) arteries (**figure 2**). Coronary angiography confirmed complete mid-LAD occlusion with reconstituted distal flow supplied via right-to-left collaterals, and 80% proximal stenosis of the OM1. He underwent successful revascularisation with two-vessel coronary artery bypass grafting and was discharged in stable condition.

Conclusion

In this paper, we review the strong evidence supporting CAC as a diagnostic and prognostic marker of ASCVD. We consider the diagnostic implications of a zero CAC score, with attention to its age-dependent limitations. In older adults, CAC=0 is a validated biomarker portending low risk of cardiovascular events.[55] However, as reflected in our illustrative case, CAC=0 does not reliably exclude obstructive CAD in younger patients, who are known to have a higher burden of non-calcified plaque. Here, CCTA is irreplaceable for guiding decision-making in both emergency and outpatient settings. When the diagnosis is in question, adults under 40 years with chest pain and an intermediate risk profile should proceed directly to CCTA. Future work will further expand our understanding of CAC scores across the demographic spectrum, facilitating optimal integration of this tool to best evaluate risk and guide interventions in the individual patient

Key messages

- The coronary artery calcium (CAC) score is a powerful, well-validated biomarker that reliably predicts risk burden in atherosclerotic cardiovascular disease
- In older adults, CAC score of zero reliably down-stratifies risk of obstructive coronary artery disease (CAD)
- In adults under 40 years, zero CAC score does not reliably exclude obstructive CAD due to higher prevalence of non-calcified plaque
- Younger patients with chest pain and risk factors raising suspicion for CAD should proceed directly to coronary computed tomography angiography (CCTA)

Conflicts of Interest

MJB is a consultant for General Electric. JP, SL, SJL, SKR: none declared.

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Patient consent

Informed patient consent was obtained for the clinical case included in this manuscript.

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