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Coronary Artery Calcium Testing in Symptomatic Patients: An Issue of Diagnostic Efficiency

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Abstract The detection and quantification of coronary artery calcification (CAC) significantly improves cardiovascular risk prediction in asymptomatic patients. Many have advocated for expanded CAC testing in symptomatic patients based on data demonstrating that the absence of quantifiable CAC in patients with possible angina makes obstructive coronary artery disease (CAD) and subsequent adverse events highly unlikely. However, the widespread use of CAC testing in symptomatic patients may be limited by the high background prevalence of CAC and its low specificity for obstructive CAD, necessitating additional testing ('test layering') in a large percentage of eligible patients. Further, adequately powered prospective studies validating the comparative effectiveness of a 'CAC first' approach with regards to cost, safety, accuracy and clinical outcomes are lacking. Due to marked reductions in patient radiation exposure and higher comparative accuracy and prognostic value make coronary computed tomographic angiography the preferred CT-based test for appropriately selected symptomatic patients.

Keywords Coronary artery calcification · Coronary calcium · Cardiac computed tomography · Coronary computed tomography angiography · Chest pain · Stress testing · Guidelines · Coronary artery disease · Coronary heart disease · Cardiovascular risk

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Introduction

Chest pain accounts for approximately 5–6 million emergency department (ED) visits and 1 in every 50 outpatient visits in the United States, ultimately costing more than $6 billion dollars in annual healthcare costs [1]. While a majority of presentations for chest pain are ultimately deemed non-cardiac in origin, in light of the substantial morbidity and mortality due to coronary heart disease, most patients undergo non-invasive testing for coronary artery disease (CAD) to better define individual cardiovascular risk. In an era of increasing focus on healthcare resource utilization, considerable interest is aimed at reducing the cost and time to provide appropriate care, ultimately identifying the right test, for the right patient, in the right clinical presentation (assuming a test is needed or indicated at all). Beyond its role as a well-established screening test for subclinical coronary atherosclerosis in asymptomatic patients, coronary artery calcium (CAC) testing has garnered increasing attention as an inexpensive, rapid, reproducible and safe alternative to exclude CAD in symptomatic patients at low-intermediate pre-test risk for obstructive coronary atherosclerosis. Current National Institute for Health and Clinical Excellence (NICE) guidelines recommend testing for CAC as the first-line examination in lower risk patients with stable chest pain symptoms [2••]. However, several potential limitations of this approach have curbed the widespread use of CAC testing in symptomatic patients and led to discordant recommendations from other professional societies. These include concerns for the presence of obstructive disease in the absence of CAC, particularly in patients at higher pre-test risk, the high background prevalence of CAC in the general population, and a low-specificity of CAC for obstructive disease, necessitating additional testing in a significant percentage of patients with evident CAC. The concern for diagnostic inefficiency due to test layering in symptomatic patients with positive CAC, as well as the ability to perform coronary computed tomographic angiography (CTA), with proven accuracy and prognostic value at radiation doses comparable to CAC testing in many patients, are prominent limitations to CAC testing in symptomatic patients in our practice. Herein, we review the evidence supporting CAC testing in symptomatic patients as well as the challenges to its widespread application.

Noninvasive Cardiac Testing – Current Approaches and Limitations

In order to understand the rationale for utilizing CAC testing in patients with symptoms concerning for angina, one must consider contextually the test performance, cost and current guideline recommendations for standard non-invasive tests for CAD (Fig. 1). Exercise stress electrocardiography (ECG) is commonly performed, relatively inexpensive, can be completed with limited support staff and does not involve ionizing radiation exposure; though it requires an interpretable electrocardiogram and an ambulatory patient. While exercise capacity remains one of the strongest indicators of long-term mortality, the diagnostic accuracy of exercise ECG is low relative to imaging-based tests for CAD. For example, based on pooled summary test performance statistics, exercise ECG has a sensitivity of 68% and specificity of 77% for the detection of obstructive CAD on invasive coronary angiography [3]. For this reason, NICE guidelines discourage the use of exercise ECG for the evaluation of patients with stable angina symptoms in patients without known CAD, despite European Society of Cardiology and American College of Cardiology Foundation / American Heart Association (ACCF/AHA) guidelines to the contrary [2••, 4, 5••]. Indeed, exercise ECG confers the only class I indication for the initial evaluation of suspected stable ischemic heart disease in intermediate risk patients with an interpretable ECG who are able to exercise [5••].

Stress echocardiography and single-photon emission computed tomography (SPECT) both improve diagnostic accuracy for the detection of obstructive coronary artery disease as compared to stress ECG at the expense of time,

	Sensitivity (%) *	Specificity (%) *	Mean Effective Radiation Dose (mSv)	Cost #	Recommendations for Initial Evaluation of Suspected Ischemic Heart Disease				
					Possible ACS ¶ [16]	Stable Symptoms [5]			
						Able to Exercise *and* Interpretable ECG		Unable to Exercise *or* Uninterpretable ECG	
						Low Probability	Intermediate Probability	Low Probability	Intermediate Probability
Stress ECG	68	77	0	$178.11		IIa	I	III	
Stress Echocardiography	85	81	0	$393.18	I	IIb	IIa	IIa	I
SPECT	88	74	10-25	$672.28		III		U	
Coronary CTA	98	89	2-10	$262.00	IIa	U	IIb	IIa ^	
CAC>0	95	50	1-3	$46.00	U	IIb			

Fig. 1 Comparison of commonly utilized non-invasive tests for coronary artery disease in patients with suspected ischemic heart disease. ACS, acute coronary syndrome; CAC, coronary artery calcium; CTA, computed tomographic angiography; ECG, electrocardiogram; mSv, millisievert; SPECT, single-photon emission computed tomography; U, uncertain. * Per-patient sensitivity and specificity for obstructive coronary artery disease defined as ≥50% coronary luminal narrowing confirmed by invasive coronary angiography according to mean values as reported in current American College of Cardiology Guidelines. Sensitivity for 'CAC=0' derived as the weighted mean from Sarwar et al. [24] and Villines et al. [34••]. # Calendar Year 2012 final Outpatient Prospective Payment System (OPPS)applying procedure codes: Stress ECG (93306), Stress Echo (93351), SPECT (78452), CAC (75571), CCTA (75574), ICA (93458). Note the coverage for coronary artery calcium scanning is limited in many regions. ¶ When follow-up 12-lead ECG and cardiac biomarkers are unremarkable. ^ In patients able to exercise CCTA meets Class IIa indication if patient (a) has continued symptoms with prior normal test findings (b) has inconclusive results from prior exercise or pharmacological stress testing, or (c) is unable to undergo stress with myocardial perfusion imaging or echocardiography

resource availability and cost. Of these, stress echocardiography has greater specificity with lower cost and no radiation, but ultimately relies on experienced technicians and readers and adequate image quality to maintain accuracy and reproducibility. While SPECT improves sensitivity for detecting significant CAD [6, 7], it remains more expensive, time consuming and incurs significant radiation, though stress only imaging may limit these drawbacks while providing sufficient negative predictive value (NPV) in low-intermediate risk patients [8].

Lastly, modern coronary CTA has proven to be the most sensitive noninvasive modality to evaluate suspected coronary artery disease in patients with stable or acute chest pain syndromes [9, 10]. While CCTA exposes patients to ionizing radiation, very low effective doses (<5 millisieverts; mSv) are now routinely achieved due to advances in scanner technology and image acquisition protocols [11]. Though CCTA requires specialized personnel and equipment that may not be widely available, data has demonstrated the potential for CCTA to reduce costs relative to standard of care primarily in its ability to reduce the time to diagnose patients in the ED setting [12]. Based on its excellent diagnostic accuracy, prognostic value [13, 14•, 15•], and potential to improve the early triage of ED patients, CCTA currently is given a class IIa indication to evaluate low-intermediate risk patients with suspected acute coronary syndrome (ACS) in whom follow-up 12-lead ECG and cardiac biomarkers are normal (Fig. 1) [16].

Coronary Artery Calcium Testing in Symptomatic Patients

As a non-invasive measure of overall coronary artery disease burden [17], CAC testing is a clinically useful screening test for coronary atherosclerosis. It is currently recommended by ACCF/AHA guidelines in select asymptomatic patients [18•] based on data demonstrating that it significantly improves risk prediction as compared to current global cardiovascular risk scores and the use of highly-sensitive C-reactive protein testing [19, 20]. Among asymptomatic screening patients, the absence of coronary calcification (CAC=0) using standard Agatston CAC scoring [21] identifies patients with extremely low rates of subsequent mortality and cardiovascular events [22–24] among patients of diverse age groups [25]. The use of CAC testing in symptomatic patients has traditionally been limited due to fundamental concerns thought to limit its accuracy and/or diagnostic efficiency that include the: (1) occurrence of coronary calcification relatively late in the atherosclerotic process ; (2) high prevalence of CAC in the population and the lack of its specificity for obstructive CAD; (3) demonstration of significant ethnic variability in plaque composition and calcification patterns; and (4) fact that high risk coronary lesions often demonstrate little or no calcification [26–31].

Diagnostic Accuracy of Absent Coronary Calcification

Studies regarding the diagnostic accuracy of CAC testing in symptomatic patients have generally reported high sensitivity and negative predictive values (NPV) for obstructive CAD in the absence of coronary artery calcification. These values compare favorably to many widely used functional tests for CAD (Fig. 1) [24]. However, as may be expected, the presence and severity of CAC has limited specificity and positive predictive value for the presence of angiographically significant CAD, generally defined as ≥50% lumen stenosis on invasive coronary angiography (ICA). Sarwar and colleagues performed a meta-analysis of 10,355 predominately symptomatic patients undergoing primarily electron-beam computed tomography (EBCT; n=8751) and demonstrated excellent sensitivity (98%) and NPV (93%) for CAC>0 when compared to blinded ICA findings among patients with stable symptoms. Within this cohort, overall specificity of CAC>0 was 40% and positive predictive value (PPV) was 68% for obstructive CAD. Based on such data, a 2007 ACC/AHA expert consensus statement [32] and recent NICE guidelines [2••] endorsed the use of CAC testing for low-risk, stable symptomatic patients, where CAC testing is used as a filter for further cardiovascular testing in a binary fashion (CAC present or absent). Specifically, patients without CAC (CAC=0) avoid further cardiovascular testing (CAD ruled out) and those with any CAC (CAC>0) receive additional testing, such as CCTA, SPECT or ICA, an approach also advocated by some expert opinion [33].

Subsequent studies utilizing multi-detector computed tomography (MDCT) scanners have similarly provided promising data demonstrating generally high, albeit variable, sensitivity and negative predictive values for binary CAC testing among symptomatic patients (Table 1). Recently, investigators from the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter registry (CONFIRM) evaluated 10,037 symptomatic low-intermediate risk patients undergoing≥64 slice CCTA and found high sensitivity and NPV for the detection of any stenosis ≥50% (sensitivity 89%, NPV 96%) and ≥70% (sensitivity 92%, NPV 99%), respectively [34••]. Within this cohort more than 13% of patients with CAC=0 had non-obstructive CAD (purely non-calcified plaque), and 3.5% and 1.4% had a stenosis ≥50% and ≥70%, respectively. Notably, in both the Sarwar analysis and CONFIRM populations, NPV remained high (>95%) despite marked differences in the prevalence of obstructive disease (≥50% stenosis), 56% and 16%, respectively.

However, in reviewing other MDCT studies, the reported sensitivity and NPV of CAC scoring in symptomatic patients are highly variable (Table 1) [35, 36, 37•, 39–41]. Examination of these studies provides a case-study for the effect of pretest probability on test performance in accordance with Bayesian principles. A sub-study of the Coronary Evaluation Using Multi-Detector Spiral Computed Tomography Angiography

Table 1 Diagnostic accuracy of coronary artery calcium using multidetector computed tomography for the detection of obstructive coronary artery disease in symptomatic patients

Author, Year [Ref]	n	Study Type and Population	Scanner/Slice Thickness	Men (%)	Mean age	CAC Prevalence n (%)		Confirmed By ICA	Prevalence ≥50% stenosis		NPV%	LR(−)
						CAC=0	CAC>0		CAC=0	CAC>0		
Haberl et al. 2005 [38]	133	Prospective observational; chest pain referred for ICA	MDCT/1.3 mm	62	67	25 (19)	108 (81)	Yes	8 (32)	45 (42)	68	0.71
Henneman et al. 2008 [39]	40	Prospective, observational; ED patients referred for ICA	MDCT	65	57	13 (33)	28 (67)	Yes	5 (38)	21 (78)	66	0.36
Akram et al. 2008 [35]	134	Retrospective; referred for ICA and CCTA	MDCT/0.6 mm	47	57	49 (64)	85 (63)	Yes	4 (8)	24 (28)	92	0.34
Gottlieb et al. 2010 [37]	291	Prospective, randomized; referred for ICA	MDCT/0.6 mm	73	59	72 (25)	219 (75)	Yes	14 (19)	149 (68)	81	0.19
Fernandez et al. 2011 [36]	225	Retrospective; ED patients	64 MDCT/0.6mm	45	53	133(59)	92(41)	No (CCTA only)	2 (1.5)	18 (20)	99	0.16
Villines et al. 2012 [34]	10,037	Prospective observational registry; referred for CCTA	≥64 MDCT	56	57	5128 (51)	4909 (49)	No (CCTA only)	180 (3.5)	1423 (29)	96	0.19
Yoon et al. 2012 [41]	136	Prospective observational; ED patients	MDCT/0.6 mm	58	56	92 (68)	44 (32)	No (CCTA only)	14 (15)	28 (64)	85	0.4
Von Ziegler et al. 2012 [40]	351	Retrospective; referred for ICA	MDCT or DSCT/0.6 mm	68	61	67 (19)	284 (81)	Yes	1 (1.5)	132 (47)	99	0.02

CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; DSCT, dual source computed tomography; ED, emergency department; ICA, invasive coronary angiography; LR(−), negative likelihood ratio; MDCT, multidetector computed tomography; NPV, negative predictive value

Using 64 Detectors (CORE 64) multi-center trial demonstrated that among 291 high risk symptomatic patients with suspected ACS, 19% of those with CAC=0 had at least one segment of ≥50% stenosis on subsequent ICA [37•]. Similarly, Henneman and colleagues cautioned against the extension of CAC in the ED setting after reporting that among 40 patients presenting with suspected ACS, 12.5% (n=5) had significant CAD in the absence of calcification [39]. Importantly, these represent smaller studies involving higher-risk patients clinically referred for ICA, a scenario where CAC scoring would generally be inappropriate; and neither study excluded patients with known CAD. In the Henneman paper, for example, 25% and 28% of patients had a prior myocardial infarction and percutaneous coronary intervention, respectively. Here, commentary by Blaha et al. regarding the use of Bayes theorem reminds us that as disease prevalence (pretest probability) increases the ability of any non-invasive test to exclude obstructive disease (sensitivity and negative predictive value) is eroded [42].

Given the discrepancy among existing heterogeneous data regarding the accuracy of binary CAC testing suggests that there is a need for prospective studies assessing the clinical outcomes, cost and safety of this approach prior to widespread clinical adoption of early CAC testing in symptomatic patients. Noting similar sentiment, in the 2012 ACCF/AHA guideline for the diagnosis of patients with potential stable ischemic heart disease, binary CAC testing in symptomatic patients was given a class IIb recommendation (level of evidence 'C': may be considered; additional studies are needed; divergence of opinion), with the writing committee stating that "additional evidence in sufficiency large cohorts of patients establishing the uncorrected diagnostic accuracy of CAC to rule in or rule out high-grade coronary artery stenosis in symptomatic patients [is] needed" [5••].

Prognostic Value of a Zero Calcium Score in Symptomatic Patients

Beyond its proven prognostic value in screening populations and its diagnostic potential in symptomatic patients to rule-out significant CAD as discussed above, the prognostic value of CAC testing in symptomatic patients warrants discussion. One of the first studies to evaluate the use of CAC scoring in symptomatic patients in the ED was performed by Georgiou and colleagues [43]. A total of 192 low-intermediate risk patients with suspected CAD underwent calcium scoring in the ED. The treating physician and patient were blinded to CAC results and subjects were followed up to 7 years. Patients with CAC=0 had an annualized event rate of 0.6% for a composite of cardiac death, stroke, myocardial infarction, revascularization and hospitalization for angina. The sensitivity and NPV for predicting any cardiac event were both 97%. The Rule Out Myocardial Infarction using Computer Assisted

Tomography (ROMICAT I) study consisted of 368 symptomatic patients undergoing CCTA and CAC scans for the evaluation of acute chest pain in the ED. Of the 14 patients (4%) with purely non-calcified plaque(s), only one (7.1%) developed ACS, a NPV for binary CAC testing of 99% [44]. Finally, from among a larger cohort study of more than 1000 patients it was shown that 60% of low-intermediate risk symptomatic patients referred for stress SPECT had a CAC score of zero, prompting the authors to conclude that these patients could have been discharged without additional evaluation [45]. Cardiac death and ACS occurred in only two (0.3%) of the 625 CAC=0 patients over a 7 month follow-up period, providing a sensitivity and NPV of 93.8% and 99.7%, respectively. On the other hand, 12 (1.2%) of 991 patients with a normal SPECT suffered an event with a sensitivity and NPV of 62.5% and 98.8% respectively (p=0.04 for sensitivity). Similar to these findings, a number of other studies attest to the prognostic reassurance provided by the absence of quantifiable CAC on non-contrast CT (Table 2) [34••, 46–53].

It is important to note that when comparing the prognostic value of CAC Agatston scores (plaque burden) versus coronary CTA, which provides angiographic measures of plaque burden, plaque composition and coronary artery stenosis, CAC scoring does not appear to provide significant additional prognostic information among symptomatic patients. Data from the CONFIRM registry [34••] and others [54] have shown that CCTA provides superior prognostic information as compared to CAC testing among symptomatic patients (Fig. 2). Additionally, among patients with obstructive (≥50% stenosis) disease on CCTA but with CAC=0 (3.5% of patients with CAC=0) within CONFIRM, there was a significant increase in cardiovascular events related to the presence of obstructive CAD (Fig. 3) [34••]. Within this important registry, there was no additional prognostic value for CCTA as compared to CAC scoring in asymptomatic patients [55]. Taken together, these observations appear to support current appropriate use criteria [56] and guidelines for the use of CT-based CAD tests [4, 5••, 16, 18•], highlighting the importance of patient symptoms in this decision-making process.

Limitations of CAC Testing in Symptomatic Patients: A Question of Diagnostic Efficiency

Based on the data discussed above, when taken in aggregate, CAC testing in symptomatic patients performs reasonably well for excluding significant CAD in symptomatic patients, based primarily on its high sensitivity and NPV. However, widespread endorsement of this approach should be cautioned for several reasons [57]. First, unlike comparable testing options, CAC scoring is a marker of CAD burden and not a direct anatomic or physiologic assessment of stenosis or ischemia, respectively, the primary features that typically guide treatment in symptomatic patients. In addition, based on the fact that calcification occurs relatively late in the atherosclerotic process, CAC testing in younger patients, in whom a smaller percentage of atherosclerosis may be calcified, may lead to false negative tests. For example, it has been reported that up to 47% of patients at autopsy during their third decade of life have identifiable coronary plaque but only about 3% of these lesions were calcified [58]. Additionally, symptomatic patients with absent CAC and significant CAD are more likely to be smokers and have a family history of premature CAD [34••]. Conversely, performance of CAC in older symptomatic patients, a cohort with higher CAC prevalence, may lead to the need for additional testing as a larger percentage of patients will have CAC>0.

Diagnostic Efficiency and Cost Considerations

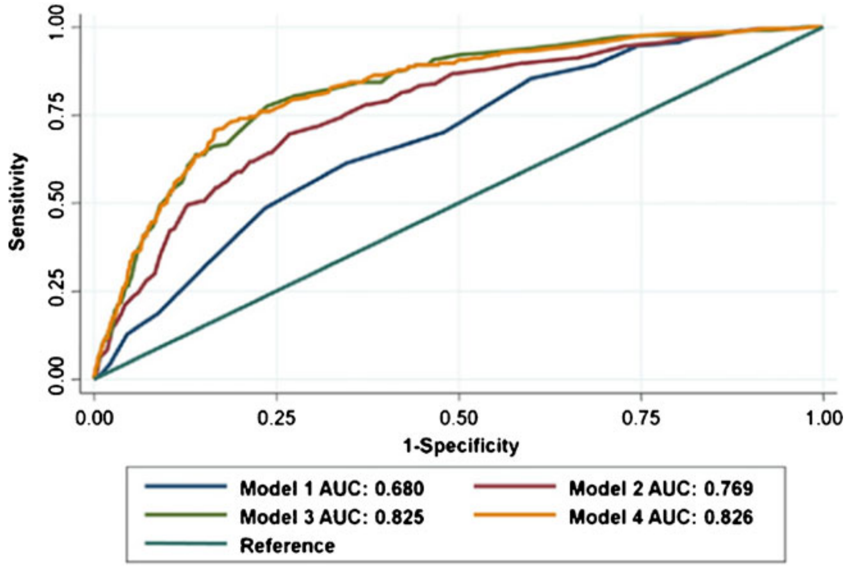
Ultimately, the primary issue that should limit the use of CAC testing in symptomatic patients is that of diagnostic inefficiency related to the high rate of additional non-invasive testing (test layering) required for patients with positive CAC when a ‘CAC first’ approach is applied in low-intermediate risk symptomatic patients. For example, from within the CONFIRM registry, a low-intermediate risk cohort that would generally qualify for CAC testing according to NICE guidelines, 49% of patients had a CAC score >0. Hence, the performance of up-front CAC scoring would have led to approximately half of all patients requiring an early secondary non-invasive test for further evaluation. In practice, we suspect that subsequent testing would generally be stress imaging tests given the limitations of exercise ECG alone, adding to evaluation costs, time to diagnosis and an increase in radiation exposure associated with radionucleotide imaging. In fact, some authors recommend direct invasive coronary angiography for those with high calcium scores (>400) despite atypical symptoms and a lack of any testing suggesting ischemia [33]. An additional consideration that favors coronary CTA as the preferred CT-based test for symptomatic patients, in addition to the improved prognostic performance and lack of significant test layering [59], is the fact that the average radiation exposure for patients undergoing coronary CTA in most experienced centers is <5 mSv and is often comparable to the effective radiation dose seen in CAC scanning.

Though several peer-reviewed cost comparisons exist for current noninvasive modalities [59–67], similar data comparing CAC to the usual care of symptomatic patients is limited. While recent NICE guidelines provide an interesting assessment of potential cost savings of a ‘CAC first’ strategy in low-risk symptomatic patients, it should be cautioned that this cost analysis was primarily aimed toward

Table 2 Prognosis of symptomatic patients evaluated for coronary artery disease according to the presence or absence of coronary artery calcification

Author, Year [Ref]	n	Type of Population	Scanner / Thickness	Men (%)	Mean age	Prevalence n (%)		Mean Follow-Up (Months)	% Lost to Follow-Up	Definition of Events (n)	Events, n (%)		NPV (%)	LR (−)
						CAC=0	CAC>0				CAC=0	CAC>0		
Detrano et al. 1996 [47]	491	Retrospective, referred for ICA	EBCT/3 mm	57	55	98 (20)	393 (80)	30	14	Cardiac death (13), MI (8)	1 (1.0)	20 (5.1)	99	0.23
McLaughlin et al. 1999 [50]	134	Retrospective, ED for chest pain	EBCT/3 mm	37	53	48 (36)	86 (64)	1	N/A	ACS (5), revascularization (3)	1(2)	7 (8.1)	98	0.34
Georgiou et al. 2001 [43]	192	Prospective observational study, ED for chest pain	EBCT/3 mm	54	53	76 (40)	116 (60)	50	8	Cardiac death (11), MI (19), revascularization (13), hospitalizations (11), stroke (4)	2 (2.6)	56 (48)	97	0.06
Keelan et al. 2001 [48]	288	Retrospective	EBCT/ 3mm	77	56	32 (11)	256 (89)	84	9	Cardiac death (N/A), MI (N/A)	1 (3.1)	21 (8.2)	97	0.39
Schmermund et al. 2004 [53]	255	Retrospective, recent onset of symptoms	EBCT/ 3 mm	71	58	62 (24)	193 (76)	42	15	Cardiac death (3), MI (2), revascularization (35)	1 (1.6)	39 (20)	98	0.09
Becker et al. 2005 [46]	924	Post ICA, no significant stenosis	MDCT	48	59	188 (20)	736 (80)	36	N/A	Cardiac death (28), MI (50)	0 (0.00)	78 (11)	100	0
Rozanski et al. 2007 [51]	1153	Referred primary care and self-referred	EBCT/MDCT 3 mm/2.5 mm	74	58	252 (22)	901 (78)	32	3	Cardiac death and MI (3), revascularizations>60 days (37)	1 (0.4)	49 (5.4)	100	0.09
Schenker et al. 2008 [52]	621	Referred for stress PET	MDCT/2.5 mm	40	61	213 (34)	408 (66)	17	0	Cardiac death (33), MI (22)	11 (5.2)	44 (10.8)	95	0.56
Hoffmann et al. 2009 [44]	368	Prospective, observational, ED for chest pain	64 MDCT/ CTA 0.6 mm	61	53	14 (3.8)	354 (86)	6.2	9.5	Cardiac death (0), MI (12), revascularization (23)	1 (7.1)	34 (9.6)	93	0.73
Laudon et al. 2010 [49]	263	Prospective, observational, ED for chest pain	EBCT / 3 mm	60	48	133 (51)	130 (49)	1, 12, 60 (mean not reported)	22 (at 5 years)	Death (0), ACS (15), revascularization (29)	1 (0.75)	45(35)	99	0.04
Nabi et al. 2010 [45]	1031	Prospective observational, ED for chest pain	MDCT/2.5 mm	40	54	625 (61)	406 (39)	7.4	1	Cardiac death (0), ACS (32)	2 (0.32)	30 (7.39)	99	0.1
Villines et al. 2011 [34••]	10,037	Observational registry referred for CCTA	≥64 MDCT	56	57	5128 (51)	4909 (49)	25	11.26	All-cause mortality (95), nonfatal MI (55), revascularization >90 days (107)	44 (0.9)	191(4.8)	99	0.36
Yoon et al. 2012 [41]	136	Prospective observational, ED for chest pain	MDCT/0.6	58	56	92 (68)	44 (32)	N/A	N/A	ACS (45)	17 (18)	28 (64)	81	0.46
Totals (mean)	15,893			56	55	6,961 (44)	8,932 (56)	30	7.73		83 (0.52)	642 (4.04)	99	0.25

ACS, acute coronary syndrome; EBCT, electron beam computed tomography; MI, myocardial infarction; N/A, not applicable; PET, positron emission tomography; other abbreviations as in Table 1



Model	AUC	SE	95% CI	P-value
1	0.680	0.0173	0.646-0.714	<0.001
2	0.769	0.0164	0.737-0.801	<0.001
3	0.825	0.0144	0.797-0.853	<0.001
4	0.826	0.0146	0.797-0.854	<0.001

Fig. 2 Receiver-operator characteristic curves: major adverse events. Receiver-operator characteristic curves of four models for predicting composite major adverse events in 8907 patients within the CONFIRM registry over a median of 2.1 years of follow-up. Model 2 (Morise score+CAC score) was superior to model 1 (symptoms and risk factors alone by Morise score), $p<0.001$. Model 3 (Morise score+number of vessels with ≥50% stenosis on CTA) was superior to model 2 (risk factors+CAC score), $p<0.001$, demonstrating superiority of CTA versus CAC for risk prediction. In addition, when CTA was added to CAC scores, event prediction was improved: Model 4 (Morise score+CAC score+number of vessels ≥50% stenosis on CTA) superior to Model 2, $p<0.001$. There was no additional value by adding CAC to models with CTA stenosis: Model 4 not superior to model 3 ($p=0.84$). AUC, area under the receiver-operator curve; CAC, coronary artery calcification; CI, confidence interval; SE, standard error. *Adapted with permission from Villines TC, et al. [34••]

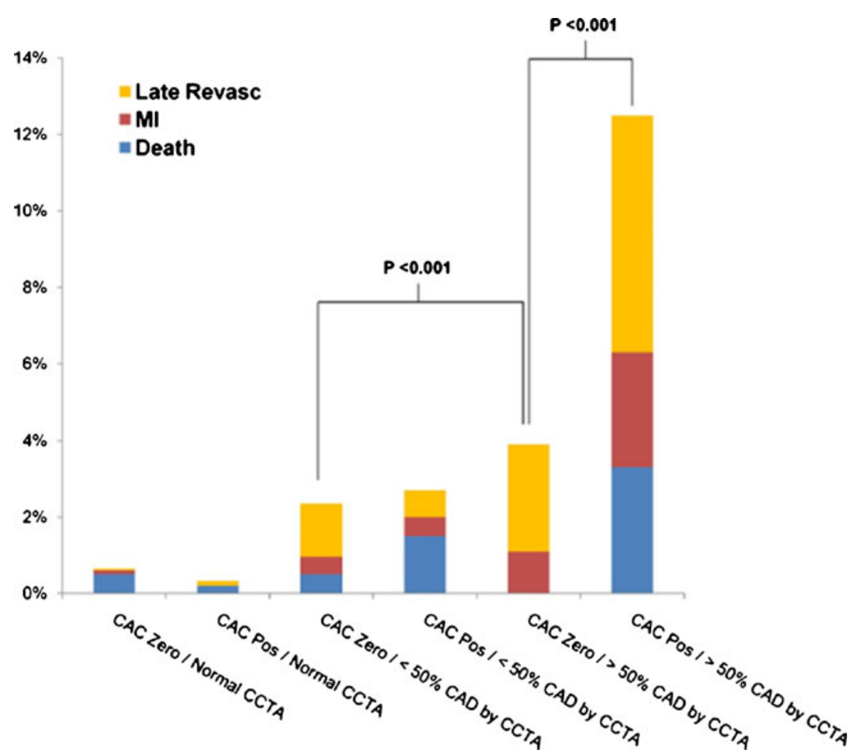


Fig. 3 Major adverse events stratified by presence of coronary artery calcification and stenosis on coronary ct angiography from the confirm registry. CAC, coronary artery calcification; CCTA, coronary computed tomographic angiography; MI, myocardial infarction; Pos, positive for CAC (CAC>0); Revasc, revascularization occurring >90 days following coronary CTA. *Adapted with permission from Villines TC, et al. [34••]

patients with stable chest pain and, thus, should not be extended to patients with acute symptoms, a touted setting for CAC application [2••]. Citing expert opinion, the NICE cost analysis assumed a sensitivity for CTA of 80% for the detection of stenosis of at least 70%, which is lower than the sensitivites included for both SPECT (86%) and CAC only (89%). This assumption ignores significant literature, including several multi-center studies of the accuracy of coronary CTA, reporting coronary CTA as the most sensitive non-invasive test for ruling out significant CAD [10].

Among patients with acute symptoms in whom CAC testing has been potentially advocated for use, we recognize that CAC testing is attractive based on its relatively low cost, reproducibility, ease of performance and interpretation, and potential use after business hours when other modalities requiring more logistical support such as stress echocardiogram, SPECT and coronary CTA may be unavailable. However, it is important to note that the binary use of CAC scanning in symptomatic patients has not been rigorously validated in a large, prospective, multicenter manner. Conversely, coronary CTA has been recently shown in several recent prospective, multi-center trials to be safe, accurate and cost-efficient when performed early for patients with acute chest pain; making it, in our opinion, the preferred testing strategy for patients with acute symptoms not at high pre-test risk who are felt to require further testing [12].

Conclusions

Coronary artery calcium testing in asymptomatic patients has been shown to significantly improve cardiovascular risk prediction beyond that provided by standard cardiovascular risk variables. Among symptomatic patients, CAC testing has generally high sensitivity and NPV for excluding significant CAD and subsequent adverse cardiovascular events when performed in low-intermediate risk patients. However, the widespread clinical application of CAC testing in symptomatic patients may be significantly limited by the high prevalence of coronary calcification in the population and low specificity of CAC for obstructive CAD, requiring high rates of additional testing to exclude significant CAD in most symptomatic populations as compared to the use of other standard non-invasive tests. In light of its potential diagnostic inefficiency and the absence of large-scale, prospective studies demonstrating the accuracy, safety and cost-effectiveness of a 'CAC-first' approach, and recognizing the progressively lower radiation doses and comparably favorable prognostic information obtained using modern coronary CTA, we feel that coronary CTA is the preferred CT-based test for symptomatic patients.

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Conflict of Interest Chad B. McBride declares no conflict of interest.
Michael K. Cheezum declares no conflict of interest.
Rosco S. Gore declares no conflict of interest.
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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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