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EXPEDITED PUBLICATION

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

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Objectives The purpose of this study was to describe the prevalence and severity of coronary artery disease (CAD) in relation to prognosis in symptomatic patients without coronary artery calcification (CAC) undergoing coronary computed tomography angiography (CCTA).

Background The frequency and clinical relevance of CAD in patients without CAC are unclear.

Methods We identified 10,037 symptomatic patients without CAD who underwent concomitant CCTA and CAC scoring. CAD was assessed as <50%, ≥50%, and ≥70% stenosis. All-cause mortality and the composite endpoint of mortality, myocardial infarction, or late coronary revascularization (≥90 days after CCTA) were assessed.

Results Mean age was 57 years, 56% were men, and 51% had a CAC score of 0. Among patients with a CAC score of 0, 84% had no CAD, 13% had nonobstructive stenosis, and 3.5% had ≥50% stenosis (1.4% had ≥70% stenosis) on CCTA. A CAC score >0 had a sensitivity, specificity, and negative and positive predictive values for stenosis ≥50% of 89%, 59%, 96%, and 29%, respectively. During a median of 2.1 years, there was no difference in mortality among patients with a CAC score of 0 irrespective of obstructive CAD. Among 8,907 patients with follow-up for the composite endpoint, 3.9% with a CAC score of 0 and ≥50% stenosis experienced an event (hazard ratio: 5.7; 95% confidence interval: 2.5 to 13.1; $p < 0.001$) compared with 0.8% of patients with a CAC score of 0 and no obstructive CAD. Receiver-operator characteristic curve analysis demonstrated that the CAC score did not add incremental prognostic information compared with CAD extent on CCTA for the composite endpoint (CCTA area under the curve = 0.825; CAC + CCTA area under the curve = 0.826; $p = 0.84$).

Conclusions In symptomatic patients with a CAC score of 0, obstructive CAD is possible and is associated with increased cardiovascular events. CAC scoring did not add incremental prognostic information to CCTA. (J Am Coll Cardiol 2011;58:2533–40) © 2011 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

CAC = coronary artery calcification

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

LR = likelihood ratio

MI = myocardial infarction

Coronary artery calcium (CAC) scoring, using noncontrast computed tomography, is a clinically useful noninvasive estimate of coronary artery disease (CAD) burden (1). Among asymptomatic patients, the absence of measurable CAC is associated with very low adverse event rates (2), and CAC scoring is endorsed as a screening test in selected individuals (3) based on a convincing body of literature demonstrating that it more precisely predicts adverse cardiovascular events compared with standard cardiovascular risk factor scoring (4). In symptomatic patients, absent CAC has been shown in several studies to have a high sensitivity and negative predictive value for excluding obstructive CAD (5), prompting a recent American College of Cardiology/American Heart Association consensus statement to endorse CAC as a "filter" for invasive angiography and/or hospital admission in patients with symptoms atypical for coronary ischemia (6). Specifically, it is recommended that CAC scoring may be used in a binary fashion (CAC present or absent) such that those without CAC may avoid further evaluation for obstructive CAD. Similarly, recent guidelines have broadly endorsed the use of CAC scoring in selected symptomatic patients (7).

Several recent studies have questioned the utility of this approach, demonstrating relatively high rates of obstructive CAD in patients with CAC scores of 0, especially among patients at high pre-test risk of obstructive CAD (8–13). The prevalence of obstructive CAD among patients with CAC scores of 0 who are at lower clinical risk of obstructive CAD, such as those referred for coronary computed tomography angiography (CCTA), has not been well studied. Additionally, the prognostic importance of obstructive CAD among patients with a CAC score of 0 and the incremental prognostic value of CAC scoring performed at the time of CCTA are unclear. The aim of the current study was to assess the prevalence and extent of CAD and clinical outcomes among a large, international registry cohort of symptomatic patients without known coronary heart disease who were referred for CCTA and found to have no measurable CAC on pre-CCTA calcium scoring. The incremental prognostic value of CAC scoring at the time of CCTA was also explored.

Methods

Patients. The CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry is an international, multicenter, observational registry collecting clinical, procedural, and follow-up data on patients who underwent ≥64-detector row CCTA between 2005 and 2009 at 12 centers in 6 countries (Canada, Germany, Italy, Korea, Switzerland, and the United States). The rationale, design, site-specific patient characteristics, and follow-up durations have been described (14). Symptomatic patients who underwent concomitant CAC scoring and CCTA were included in the present analysis. Individuals with known CAD (previous myocardial infarction [MI] and/or coronary revascularization) were excluded. Institutional review board approval was obtained at each center.

As previously described (14), we prospectively collected information on the presence of cardiovascular risk factors in each individual. Chest pain was classified according to the methods of Diamond and Forrester (15). CAC was quantified according to the Agatston method (16).

Patient preparation, CCTA data acquisition, and clinical result reporting were done according to Society of Cardiovascular Computed Tomography guidelines (17). Image interpretation was performed in a uniform fashion at each site according to Society of Cardiovascular Computed Tomography guidelines (18) by highly experienced imagers who were level III equivalent and/or board certified in cardiovascular computed tomography. Coronary atherosclerotic lesions were quantified for lumen diameter stenosis by visual estimation and graded as none (0% luminal stenosis), mild (1% to 49%), moderate (50% to 69%), or severe

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Table 1 Baseline Characteristics and CCTA Results Stratified According to the Detection of CAC (N = 10,037)

	CAC Score = 0 (n = 5,128)	CAC Score >0 (n = 4,909)	p Value
Age, yrs	52 ± 12	61 ± 11	<0.001
Male	43	56	<0.001
Hypertension	44	59	<0.001
Diabetes	9	18	<0.001
Hypercholesterolemia	51	62	<0.001
Smoking	16	18	0.718
Family history of premature CAD	29	33	<0.001
Pre-test probability of obstructive CAD*	32% (42)	54% (49)	<0.001
Typical angina	13	16	<0.001
Dyspnea	26	37	<0.001
CAC score	0 (0)	90 (278)	<0.001
CCTA results: worst stenosis			
Normal coronaries	84	19	<0.001
Nonobstructive (1%–49%)	13	52	<0.001
Obstructive (≥50%)	3.5	29	<0.001
Obstructive, severe (≥70%)	1.4	16	<0.001
CCTA: no. of vessels with ≥50% stenosis			
1	2.8	17	<0.001
2	0.4	8	<0.001
3	0.2	3.3	<0.001
Left main	0.3	1.6	<0.001

Values are mean ± SD, %, or median (interquartile range). *Defined according to the method of Diamond-Forrester.

CAC = coronary artery calcification; CAD = coronary artery disease; CCTA = coronary computed tomography angiography.

(≥70%). Coronary lesions ≥50% in lumen stenosis severity were defined as obstructive.

Follow-up and outcomes. The primary clinical endpoint was time to death of any cause among patients from all 12 CONFIRM sites. In patients with complete follow-up for MI and coronary revascularization, a secondary analysis was performed assessing time to a composite endpoint consisting of all-cause mortality, nonfatal MI, and coronary revascularizations performed ≥90 days after CCTA. Coronary revascularizations ≥90 days after CCTA were defined as late, given our group's previous demonstration that early revascularizations are generally invoked by scan findings, whereas late revascularizations are generally associated with disease worsening (19). Early revascularizations (<90 days from CCTA) were reported separately as an outcome of clinical interest.

Statistical analysis. Categorical variables are presented as frequencies with percentages and evaluated using the chi-square test. Continuous variables are presented as mean ± 1 SD or median (interquartile range) and were evaluated using a Student unpaired *t* test or a Mann-Whitney *U* test, as appropriate. Cumulative event-free survival was assessed using the Kaplan-Meier method and compared with the log rank test. Multivariable analyses were calculated with the Cox proportional hazard model (with 95% confidence intervals), adjusted for differences in symptoms and clinical cardiovascular risk factors. Variables associated with the presence of obstructive CAD were assessed using univariable and multivariable logistic regression. To assess for potential site-specific differences that may have limited pooling of data and outcomes, we included site as a covariate in each univariable and multivariable model and demonstrated that there was no significant change in any of the results. In addition, a series of interaction tests were performed by site demonstrating no significant influence of potential site-specific differences. To assess the incremental prognostic value of calcium score and CCTA with respect to baseline risk factors, Cox models were compared using clinical risk factors for obstructive CAD calculated as the Morise score (20), the Morise score plus CAC score (categorized as zero calcium, ≤100, 101 to 400, and >400), Morise score plus CCTA (categorized as no disease, <50% worst stenosis, 1-vessel obstructive disease, 2- or 3-vessel/left main CAD), and Morise score plus CCTA and CAC. Receiver-operator characteristic curves were prepared for each of the models and compared using the Delong method (21). Statistical significance was accepted for 2-sided p values <0.05. All calculations were performed using STATA version 11.0 (StataCorp, College Station, Texas).

Results

The CONFIRM registry, consisting of 27,125 patients, was screened and 10,037 symptomatic patients without known CAD who underwent both CAC scoring and CCTA were identified. The mean age of patients in the cohort was 57 ±

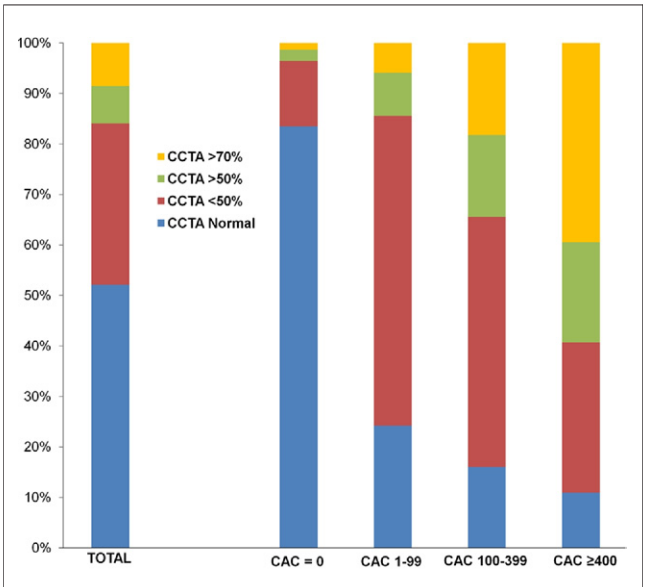

Figure 1 Coronary Artery Stenosis on CCTA

Increasing frequency of obstructive disease with increasing coronary artery calcification (CAC) (Agatston) scores is demonstrated. *p < 0.001 between groups. CCTA = coronary computed tomography angiography.

Table 2 Univariable and Adjusted Multivariable Predictors of the Presence of ≥50% Coronary Stenosis on CCTA Among Patients With a CAC Score of 0 (n = 4,738)

	Univariable (Crude)			Multivariable (Adjusted)*		
	OR	95% CI	p Value	OR	95% CI	p Value
Age*	1.05	1.04–1.06	<0.001	1.05	1.04–1.07	<0.001
Male*	1.36	1.01–1.82	<0.045	1.93	1.33–2.78	<0.001
Body mass index	1.04	1.01–1.06	0.004	1.02	0.99–1.06	0.14
Hypercholesterolemia	1.46	1.08–1.98	0.014	1.13	0.79–1.61	0.51
Diabetes	2.51	1.72–3.66	<0.001	1.58	0.97–2.57	0.068
Family history of premature CAD*	2.35	1.74–3.18	<0.001	2.31	1.60–3.30	<0.001
Hypertension	1.15	0.85–1.55	0.35			
Smoking*	1.45	1.00–2.09	0.47	1.72	1.12–2.64	0.013
Chest pain						
Nonanginal	1.05	0.67–1.63	0.84			
Atypical	0.84	0.60–1.18	0.32			
Typical	1.26	0.83–1.90	0.27			
Dyspnea*	1.80	1.27–2.56	0.001	1.57	1.08–2.27	0.017

*Variables significantly predictive of ≥50% stenosis on CCTA in the adjusted logistic regression model.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

12 years, and 56% of patients were male. Detailed patient characteristics and CCTA results are shown in Table 1, stratified according to the presence or absence of detectable CAC on pre-CCTA calcium scanning. Among the 10,037 patients included in this analysis, 51% (n = 5,128) had a CAC score of 0. Patients with a CAC score of 0 were younger and more likely female and had a lower burden of cardiovascular risk factors compared with subjects with detectable CAC (CAC score >0).

Patients with increasing degrees of CAC had significantly increased severity of angiographic CAD on CCTA (Fig. 1). In patients with a CAC score of 0, 16% of patients had evidence of some degree of CAD on CCTA, with 13% of patients with a CAC score of 0 having nonobstructive CAD (<50% stenosis). The prevalence of any major epicardial vessel with ≥50% and ≥70% stenosis on CCTA among patients with a CAC score of 0 was 3.5% and 1.4%, respectively. The majority of patients with a CAC score of 0 and obstructive CAD (n = 180) had single-vessel disease (82%), with a lower prevalence of 2-vessel (12%), 3-vessel (6%), and left main (0.3%) disease. Using a 15-segment coronary artery tree model, patients with a CAC score of 0, and evidence of any CAD, the median number of segments exhibiting any degree of plaque in patients with a CAC score of 0 was 2 (interquartile range, 2).

For the detection of any stenosis ≥50% on CCTA, the presence of measurable CAC (CAC score >0) on calcium

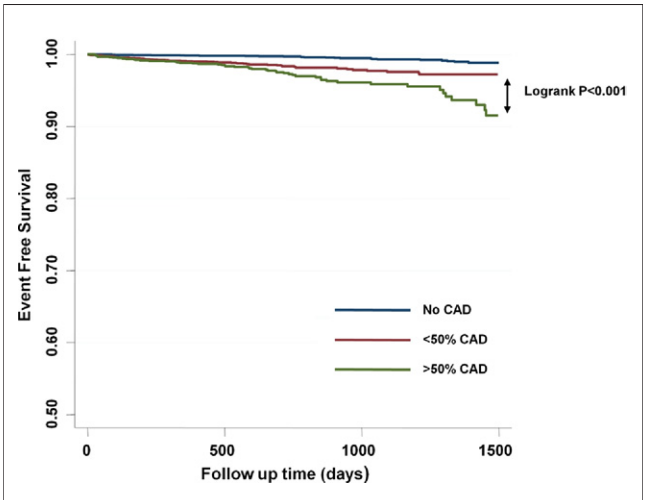

Figure 2 All-Cause Mortality-Free Survival

Survival among all patients according to worst coronary artery stenosis on coronary computed tomography angiography demonstrating decreased survival among patients with at least 1 major epicardial vessel with ≥50% stenosis. CAD = coronary artery disease.

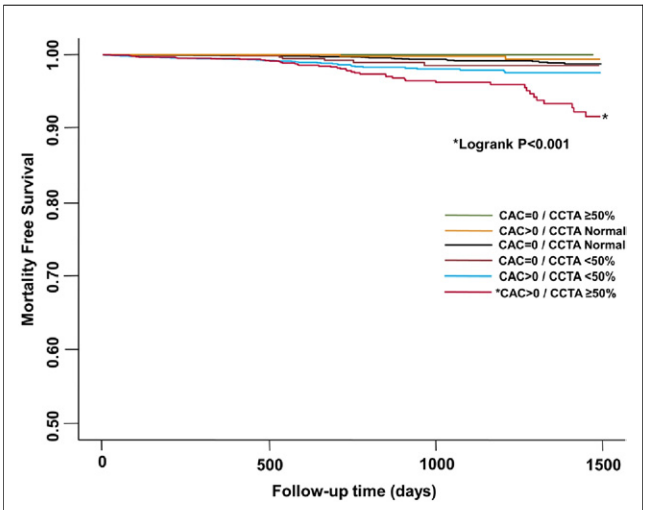

Figure 3 Survival According to CAC Score and Stenosis Severity

All-cause mortality-free survival among patients according to CAC score and the severity of coronary artery disease on coronary CCTA. Abbreviations as in Figure 1.

Table 3 Early* Revascularization Rates Among Patients With and Without CAC Stratified by Stenosis Severity on CCTA

	CCTA Results				
CAC score = 0 (n = 4,738)	No CAD (n = 3,915)	<50% stenosis (n = 646)	≥50% stenosis (n = 177)	≥70% stenosis (n = 67)	p Value
Early revascularization	0.1 (4)	0.77 (5)	22 (39)	34 (23)	<0.001
CAC score >0 (n = 4,169)	No CAD (n = 826)	<50% stenosis (n = 2,156)	≥50% stenosis (n = 1,187)	≥70% stenosis (n = 638)	p Value
Early revascularization	1.2 (10)	0.97 (21)	29 (342)	44 (278)	<0.001
p Value (CAC score: 0 vs. >0)	<0.001	0.65	0.06	0.15	

Values are % (n). *Occurring <90 d after CCTA.
Abbreviations as in Table 1.

scoring demonstrated a sensitivity of 89%, specificity of 59%, negative predictive value of 96%, and positive predictive value of 29%. When using a threshold of ≥70% stenosis for obstructive CAD, a CAC score >0 demonstrated a sensitivity, specificity, negative predictive value and positive predictive value of 92%, 55%, 99%, and 16%, respectively. The positive likelihood ratio (LR) for a CAC score >0 to predict ≥50% stenosis was 2.14; the negative LR was 0.19. The positive LR for a CAC score >0 to predict a ≥70% stenosis was 2.04; the negative LR was 0.15. In receiver-operator characteristic analysis, the presence of any CAC (compared with a CAC score of 0) significantly increased the area under the curve (for the prediction of detecting a stenosis from 0.74 to 0.82 ($p < 0.01$).

Univariable and multivariable predictors of obstructive CAD on CCTA among patients with a CAC score of 0 are shown in Table 2. After multivariable risk adjustment, obstructive CAD in these patients was associated with the traditional cardiovascular risk factors of increasing age, male sex, and smoking. The strongest independent predictors of obstructive CAD among patients without CAC were a family history of premature CAD among a first-degree relative and smoking. Typicality of angina pectoris did not discriminate individuals with a CAC score of 0 who did versus did not have obstructive CAD, but dyspnea as a presenting symptom was highly associated with the presence of obstructive CAD on CCTA (adjusted odds ratio: 1.57; 95% confidence interval: 1.08 to 2.27; $p = 0.017$).

Mortality and adverse events. Among the entire cohort (n = 10,037), during a median follow-up of 2.1 (interquartile range, 2.0) years, patients with any obstructive CAD by CCTA experienced a significantly increased rate of all-cause mortality (Fig. 2). When restricted to individuals with a CAC score of 0, there was no difference in all-cause mortality despite the presence of nonobstructive or obstructive CAD (Fig. 3).

Among the 8,907 patients with complete follow-up for the secondary endpoints of coronary revascularization and MI, patients with evidence of obstructive CAD had significantly increased rates of early coronary revascularization, both among patients with and without coronary artery calcification (Table 3).

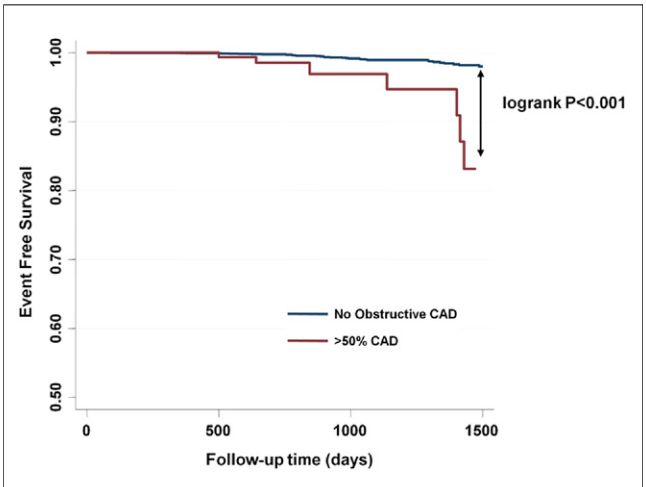

Figure 4 Survival Among Patients With a CAC Score of 0

Decreased event-free survival from major adverse events (all-mortality, nonfatal myocardial infarction, or coronary revascularization) among patients without detectable CAC but ≥50% stenosis on coronary computed tomography angiography. Abbreviations as in Figures 1 and 2.

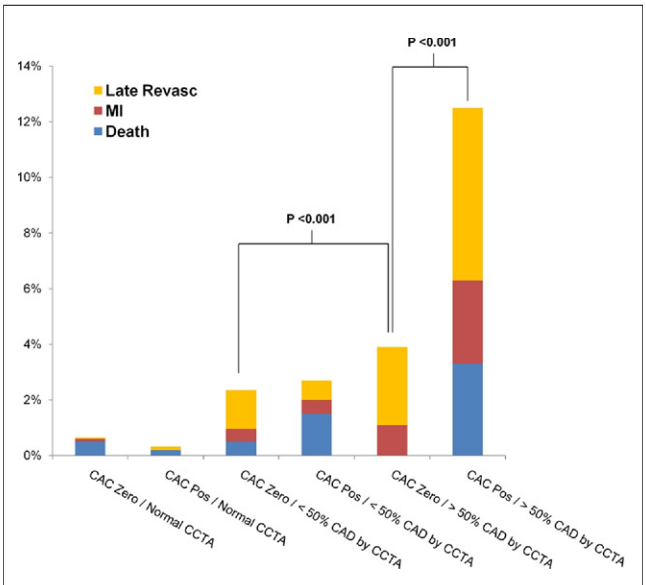

Figure 5 Major Adverse Events Stratified by CAC Score and Stenosis

Major adverse events stratified by the presence (pos) or absence (zero) of CAC and ≥50% stenosis on CCTA. MI = myocardial infarction; Revasc = revascularization; other abbreviations as in Figures 1 and 2.

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Table 4 Adverse Events Among Patients From 8 Sites With Composite Endpoint Assessment for MAE During a Median Follow-up of 2.1 Years

	Combined MAE	Death	MI	Late Revascularization
CAC score of 0 (n = 4,738)	0.9 (44)	0.4 (21)	0.2 (9)	0.34 (16)
No CAD (n = 3,915)	0.6 (24)	0.5 (18)	0.1 (4)	0.05 (2)
<50% stenosis (n = 646)	2.0 (13)	0.5 (3)	0.5 (3)	1.4 (9)
≥50% stenosis (n = 177)	3.9 (7)	0% (0)	1.1 (2)	2.8 (5)
p Value (within a CAC score of 0 for increasing CAD)	<0.001	0.7	0.002	<0.001
CAC score >0 (n = 4,169)	4.8 (191)*	1.8 (74)	1.1 (46)	2.2 (91)
No CAD (n = 826)	0.4 (3)	0.2 (2)	0 (0)	0.1 (1)
<50% stenosis (n = 2,156)	2.5 (54)	1.5 (33)	0.5 (11)	0.7 (16)
≥50% stenosis (n = 1,187)	11.3 (134)*	3.3 (39)	3.0 (35)	6.2 (74)
p Value (within a CAC score >0 for increasing CAD)	<0.001	<0.001	<0.001	<0.001

Values are % (n). *$p < 0.05$ compared with patients with a CAC score of 0.
MAE = major adverse events (all-cause mortality, nonfatal MI, or coronary revascularization occurring 90 days after testing); MI = myocardial infarction; other abbreviations as in Table 1.

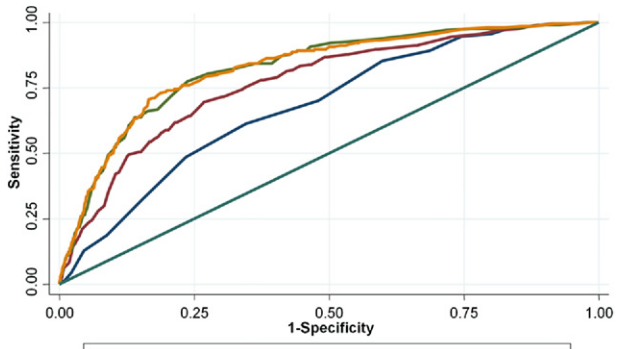
For the composite prognosis endpoint of death, nonfatal MI, or late coronary revascularization, significantly higher rates of major adverse events were observed for patients with a CAC score of 0 and obstructive CAD on CCTA compared with patients with a CAC score of 0 and no or nonobstructive CAD (Fig. 4). Specifically, during follow-up, 3.9% (7 of 177) of patients with a CAC score of 0 and ≥50% stenosis experienced an adverse event compared with 0.8% of patients with a CAC score of 0 and no obstructive CAD ($p < 0.001$). After multivariable adjustment, the presence of obstructive CAD conferred an increased hazard ratio for a combined adverse event by 5.7 (95% confidence interval: 2.5 to 13.1; $p < 0.001$). This difference was primarily driven by an increase in late coronary revascularizations (5 of 7 events) (Fig. 5, Table 4).

Comparative prognostic value of clinical variables, CAC scoring and CCTA. Hazard ratios, unadjusted and adjusted for Morise risk score categories, for the composite outcome of all-cause mortality, nonfatal MI, and late coronary revascularization are shown in Table 5. Increasing CAC scores, the presence of nonobstructive CAD, any stenosis ≥50%, and the number of coronary territories with ≥50% stenosis were independently predictive of adverse events. Receiver-operator characteristic curves to determine the predictive value of clinical risk factors (Morise score: model 1); Morise score + CAC scoring (model 2); Morise score + CCTA (number of vessels with obstructive disease: model 3); and Morise score + CAC + CCTA (model 4) were directly compared. The addition of CAC scoring and the presence and severity of CAD on CCTA each incrementally improved the

Table 5 Hazard Ratios for the Composite Outcome of All-Cause Mortality, Nonfatal MI, and Late Revascularization According to Morise Risk Score, CAC Score, and CCTA

	Unadjusted Model			Risk Factor-Adjusted Model		
Variable (N = 8,907)	HR	95% CI	p Value	HR	95% CI	p Value
Morise risk category						
Low (1–8)	1.00					
Intermediate (9–15)	3.71	1.73–7.97	0.001			
High (16–24)	6.32	2.97–13.5	<0.001			
CAC score model						
0	1.00			1.00		
1–100	3.08	2.07–4.58	<0.001	2.82	1.83–4.35	<0.001
101–400	9.39	6.42–13.7	<0.001	7.16	4.66–11.0	<0.001
>400	13.90	9.52–20.4	<0.001	9.78	6.29–15.2	<0.001
CCTA models						
Presence of ≥50% CAD						
None or <50% CAD	1.00			1.00		
≥50% CAD	8.47	6.70–10.7	<0.001	7.10	5.40–9.33	<0.001
No. of involved vessels						
None (no CAD)	1.00			1.00		
<50% stenosis	5.48	3.63–8.28	<0.001	4.19	2.63–6.68	<0.001
1-vessel disease (≥50% stenosis)	16.90	11.2–25.4	<0.001	13.50	8.52–21.4	<0.001
2-vessel disease	26.50	17.0–41.5	<0.001	20.70	12.6–33.9	<0.001
3-vessel and/or left main disease	32.50	20.2–52.2	<0.001	27.10	16.0–45.9	<0.001

HR = hazard ratio; other abbreviations as in Tables 1, 2, and 4.



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

Figure 6 **Receiver-Operator Characteristic Curves: Major Adverse Events**

Receiver-operator characteristic curves of 4 models for predicting composite major adverse events in 8,907 patients over a median of 2.1 years. CAC score categories were defined as: 0, ≤100, 101 to 400, and >400. Model 2 (Morise score + CAC category) compared to Model 1 (Morise score only): $p < 0.001$. Model 3 (Morise score + number vessels ≥50% stenosis) compared to Model 2 (Morise score + CAC category): $p < 0.001$. Model 4 (Morise score + CAC category + number vessels ≥50% stenosis) compared to Model 2 (Morise score + CAC category): $p < 0.001$. Model 3 compared to Model 4: $p = 0.84$. AUC = area under the curve; CAC = coronary artery calcification; CI = confidence interval.

ability to predict future adverse events beyond clinical risk factors alone. The number of vessels with obstructive CAD (model 3) was superior to CAC scoring (model 2) for the prediction of major adverse events (Fig. 6). CAC scoring performed at the time of CCTA resulted in no incremental improvement in predicting composite adverse events compared with clinical risk factors and CCTA alone (model 3 vs. model 4, $p = 0.84$).

Discussion

In this large, multicenter, international cohort without known CAD, clinically referred for noninvasive coronary angiography, the absence of measurable CAC significantly reduced, but did not fully exclude, the presence of obstructive CAD on current generation CCTA. CAC scoring has been advocated as a quick, noninvasive, iodinated contrast-free method to assess for the likelihood of obstructive CAD in symptomatic patients (6,7) based on studies demonstrating very low rates of obstructive disease in patients with a CAC score of 0 (5). However, recent studies have shown significantly higher rates of obstructive CAD in patients with a CAC score of 0, ranging from 7% to 38% of patients (8–13), especially when studied in patients with higher risk presentations, consistent with Bayesian reasoning. The prevalence of significant CAD in patients with a CAC score of 0 primarily at intermediate pre-test risk in the current study was lower than many of these recent reports, reaffirming the importance of properly assessing patient pre-test probability for obstructive CAD if CAC scoring were to be used in symptomatic patients, as endorsed by current expert statements and guidelines (6,7).

The finding of increased rates of late coronary revascularizations among patients with a CAC score of 0 and ≥50% stenosis on CCTA but no difference in mortality is not surprising. The majority of patients with a CAC score of 0 and obstructive disease had single-vessel disease, a cohort in which coronary revascularization has not been shown to improve survival. Also, due to the low-intermediate risk population studied in this analysis, longer term follow-up durations may be needed to fully assess the prognostic value of nonobstructive CAD, and the potential impact of preventive therapies (e.g., statins).

Viewed positively, CAC scoring (CAC score of 0) significantly reduced the likelihood of finding significant CAD on CCTA. However, CAC scoring as an initial diagnostic test, applied in a binary fashion in which a CAC score of 0 results in no further testing and a CAC score >0 is followed by additional testing, would have resulted in 3.5% of patients without an appropriate initial diagnosis of obstructive CAD who are at increased risk of intermediate-term adverse events and a large percentage of patients (those with a CAC score >0) requiring further testing. The performance of CAC scoring at the time of CCTA, although often done to assist in CCTA scan acquisition planning (e.g., identification of dense calcification that may change scan acquisition parameters), did not add incremental prognostic value beyond clinical data and disease severity by CCTA.

Study limitations. The definition of CAD was made using CCTA and not invasive coronary angiography; therefore, the possibility of false-positive and false-negative CCTA findings exists despite the performance of CCTA by international experts. We also recognize that patients diagnosed with obstructive CAD on CCTA are more likely to undergo revascularization, especially early after testing. We attempted to control for this by censoring early revascularizations from the composite endpoint. Differences in the application of medical therapies after CCTA were not assessed and may have affected patient outcomes. Finally, we did not assess individual coronary plaque characteristics, such as the degree of vessel remodeling, which may improve the prognostic yield of CCTA (22).

Conclusions

In symptomatic patients referred for CCTA, the absence of CAC reduces but does not fully eliminate the occurrence of obstructive CAD. Among patients without CAC, the presence of at least 1 coronary artery stenosis ≥50% is predictive of increased rates of late coronary revascularizations and nonfatal MIs during an intermediate-term follow-up period. CAC scoring performed at the time of CCTA in an intermediate-

risk population does not appear to offer significant incremental prognostic information when combined with clinical risk factors and CAD severity on CCTA.

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Key Words computed tomography ■ coronary artery disease ■ coronary calcium score ■ coronary computed tomography angiography ■ prognosis.