Title

Point of Care Clinical Risk Score to Improve the Negative Diagnostic Utility of an Agatston Score of Zero

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ıical Risk Score to Improve the Negative Diagnostic Utility of an Agatston Score =0: Averting the need for Coronary CT angiography

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Abstract

Background

Coronary artery calcification (CAC) is a marker of underlying atherosclerotic vascular disease. Absence of CAC is associated with a low prevalence of obstructive coronary artery disease (CAD), but it cannot be ruled out completely. We sought to develop a clinical tool that can be added to Agatston score =0 to rule out obstructive CAD with high accuracy.

Methods

We developed a clinical score retrospectively from a cohort of 4,903 consecutive patients with an Agatston score =0. Patients with prior diagnosis of CAD, coronary percutaneous coronary intervention (PCI) or surgical revascularization were excluded. Obstructive CAD was defined as any epicardial vessel diameter narrowing of ≥ 50%. The score was validated using an external cohort of 4,290 patients with an Agatston score =0 from a multinational registry.

Results

The score consisted of 7 variables: age, sex, typical chest pain, dyslipidemia, hypertension, family history and diabetes mellitus. The model was robust with an area under the curve of 0.70 (95% confidence interval [CI]: 0.65-0.76) in the derivation cohort and 0.69(95% CI:0.65-0.72) in the validation cohort. Patients were divided into three risk groups based on the score, low (≤6), intermediate (7-13) and high (≥ 14). Patients who score ≤6 have a negative likelihood ratio of 0.42 for obstructive CAD, while those who

score ≥14 have a positive likelihood ratio of >5.5 for obstructive CAD. The outcome was ruled out in >98% of patients with a score≤6 in the validation cohort.

Conclusion

We developed a score that can be used to rule out obstructive CAD in patients with an Agatston score =0 with high confidence.

Keywords:

Computed tomographic angiography, obstructive coronary artery disease, risk score

Abbreviations:

CAC: Coronary artery calcification

CAD: Coronary artery disease

CCTA: Coronary computed tomographic angiography

ROC: Receiver operating characteristics

Short Commentary (250) Words

Traditionally, coronary artery calcium (CAC) scoring has been using in the asymptomatic population to refine risk of future adverse cardiovascular events. Most recently, the AHA issued guidelines for therapy based on CAC. The utility of CAC in the symptomatic population and how it may be used to guide downstream testing is lacking. The results of our study suggest that the combination of a clinical model and CAC =0 may effectively eliminate the need of additional testing. A prospective trial is needed to verify these results.

INTRODUCTION

Coronary artery calcification (CAC) is a marker of underlying coronary artery atherosclerosis and an independent predictor of future cardiovascular events.[1-4] The absence of CAC is prognostically important and identifies a population at low risk of future cardiovascular events.[1,2,5-9] Despite the low rates of future cardiovascular events, the absence of CAC does not have sufficient negative predictive value (NPV) for widespread use as a single test for clinical risk stratification among symptomatic patients for whom there is a suspicion of obstructive CAD.[10]

Previous studies have demonstrated that, despite the absence of CAC, 1.4-7% of symptomatic individuals have obstructive CAD.[11-13] Thus, clinicians are often unwilling to use the absence of CAC to halt additional testing in symptomatic patients with suspected CAD.

Image acquisition for CAC is routinely performed prior to coronary computed tomographic angiography (CCTA) and quantified using the Agatston method.[14] We sought to derive and validate a clinical tool that can be used in symptomatic patients without CAC (Agatston Score = 0) to help to rule out obstructive CAD and potentially limits unnecessary downstream testing .

METHODS

STUDY DESIGN & ELIGIBILITY

Using a cardiac computed tomography (CT) registry[15], we identified a derivation cohort comprised of patients with an Agatston Score = 0 who also underwent coronary CT angiography (CCTA). A non-overlapping subgroup from CONFIRM registry with Agatston score = 0 was used for validation.[16] We included only CONFIRM centers with complete CCTA data and data on chest pain typicality and cardiac risk factors. Patients with a history of coronary artery disease, myocardial infarction or revascularization were excluded. Additionally, we excluded patients being worked up for acute presentation with chest pain or to rule out acute coronary syndrome.

The study was approved by our institutional review board and written, informed consents were obtained by all enrolled patients. Data supporting the findings of this study may be available from the corresponding author upon reasonable request.

CLINICAL DEFINITIONS

Clinical assessment done at the time of CCTA included medical history, physical findings and available laboratory studies.[15,16] Chest pain typicality was defined according to the classification proposed by Diamond and Forrester.[17] The presence of cardiac risk factors was obtained through patient self-reporting and/or medical records. Hypertension was defined as known history of diagnosis of hypertension (systolic blood pressure ≥140 mmHg) or being treated for hypertension. Diabetes mellitus was defined as history of type I or type II diabetes or the use of hypoglycemic agents. Dyslipidemia was defined as a self-reported history of a known diagnosis of dyslipidemia

or treatment with lipid lowering agents. Family history of CAD was defined as diagnosis of CAD in a first-degree relative (age of ≤55 years for men and ≤65 years for women).

The pre-test probability of obstructive CAD (≥ 50% luminal stenosis) was calculated for all patients according to age, sex and typicality of chest pain using updated Diamond-Forrester risk model.[18]

CORONARY CALCIFICATION AND COMPUTED TOMOGRAPHY ANGIOGRAPHY

CAC and CCTA images were acquired using single or dual source ≥ 64 slice CT scanners.[15,16] Scans were interpreted by physicians experts at each site.[19,20] Coronary calcification was quantified using the Agatston method.[14] Coronary artery segmental luminal diameter was graded on 4-point score (normal, mild (<50% stenosis), moderate (50-69% stenosis), or severe (≥70% stenosis)) and patients with a stenosis of ≥50% were categorized as having obstructive CAD. Since most of our data were collected prior to the publication of the Coronary Artery Disease-Reporting and Data System (CAD-RAD), minimal (1-24%) and mild (25-49%) stenosis were grouped together as a mild stenosis (0-49%).[10]

STATISTICAL ANALYSIS

To compare the clinical characteristics of patients, we used Fisher's exact test for categorical variables and t-test for continuous variables. Categorical variables are presented as proportions with percentages and continuous variables are presented as means with standard deviations. Statistical significance threshold was set at $p < 0.05$. Multiple imputations

were performed for the missing values. Centers with large proportions of missing data on chest pain typicality or any of the risk factors for CAD were excluded from the validation cohort. All statistical procedures were performed using SAS 9.4© statistical software (SAS institute, Cary, NC, USA.).

Model Derivation

To avoid data-driven model development, we specified our clinical variables apriori.[21] A group of practicing cardiologists was surveyed for 5-10 clinical predictors from a list of candidate clinical variables with potential association with CAD. This list included demographic data, known diagnoses and risk factors, symptoms, medications, physical assessment and electrocardiographic findings. Clinical variables with highest number of votes (age, sex, typical chest pain, hyperlipidemia, hypertension, diabetes mellitus, current smoking and family history) were included in a multivariable logistic regression model. Interaction between gender and other variables in the multivariable model was examined. Receiver operating characteristic (ROC) curve for the multivariable model was generated. The discriminative ability of the model was assessed using area under the curve (AUC) and the corresponding c statistics. Model's goodness of fit was assessed using Hosmer-Lemeshow statistics.

Development of the Scoring System

A point scoring system was derived from the proposed multivariable model based on the regression coefficients. We assigned points for each

variable according to its regression coefficient, with 1 point for the smallest regression coefficient which served as the least common denominator for assigning point values for the score items. We then computed the score for each patient and evaluated the classification ability of the developed score using the sensitivity, specificity, positive and negative predictive values and the likelihood ratios with confidence intervals of each level of the score. The calibration of the score was assessed by plotting the predicted risk of obstructive CAD against the observed one. The goodness of fit of the developed score was assessed using Hosmer-Lemeshow statistics where p value >0.05 indicates adequate fit of the score.

Score Validation

We applied the score externally and assessed the applicability of the scoring system in the validation cohort. We calculated the proportion of patients classified by the developed score and the observed risk of obstructive CAD for each risk group in the derivation and validation cohorts. We calculated the risk of all-cause mortality for each risk group in the validation cohort based on data of a median follow up of 2 years.

RESULTS

A total of 44,125 consecutive patients (17,000 from the derivation cohort registry, and 27,125 patients from the CONFRIM registry representing the validation cohort) were screened. After excluding patients with a history of CAD, coronary revascularization, cardiac transplantation, and congenital

heart disease; we identified 4,903 eligible patients with an Agatston score = 0 in the derivation cohort, with 2.3% (n=112) having obstructive CAD (diameter stenosis ≥50%). A non-overlapping 8,021patients from CONFIRM registry were found with an Agatston score = 0. Centers with a large proportion of missing data were excluded. The final validation cohort comprised of 4,290 patients, with 4.8% (n=207) having obstructive CAD (Table 1). The proportion of imputed data was less than 5% of the total observations in both derivation and validation cohorts.

Derivation Cohort

The pre-specification survey resulted in selection of: age, sex, typical chest pain, family history, dyslipidemia; hypertension and diabetes mellitus to be included in the multivariable logistic regression model (Table 2). Current smoking was excluded from the multivariable model due to the resulting paradoxical association between smoking and the outcome of obstructive CAD, which is clinically non-plausible. There was insignificant interaction between sex and other variables. The proposed model had an area under the ROC curve of 0.70 (95% CI:0.65-0.76) in the derivation cohort (Figure 1A).

Score Development

Each variable was assigned a value derived from the corresponding regression coefficient in the multivariable model (Table 3). Based on the generated score (range = 0-20), the predicted probability for prevalence of obstructive CAD ranged from 0.45% (95% CI: 0.26-0.77) to 18% (95%CI:

10.78-28.30). The diagnostic ability for each score threshold in the model was calculated (Table 4) and thresholds were grouped into three categories (low (≤ 6), intermediate (7-13) and high (≥ 14)) based on the positive and negative likelihood ratios (Table 5). Patients with a score of ≤ 6 have a high negative predictive value (99%) and a low negative likelihood ratio (0.42) (Table 5). Conversely, patients for whom the score was ≥ 14 have a specificity of 98% and a positive likelihood ratio of > 5 for obstructive CAD (Table 5).

SCORE VALIDATION

Using an external validation cohort, the score demonstrated an acceptable discriminative performance with an area under ROC curve of 0.69 (95%CI: 0.65-0.72) (Figure 1B). The proportion of patients in each risk category in the validation cohort is similar to that in the derivation cohort, but slightly higher prevalence of obstructive CAD consistent with the overall higher prevalence of obstructive CAD in the validation cohort (Table 5). The score had a good calibration between predicted and observed risks of obstructive CAD in the derivation and validation cohorts particularly at low and intermediate risk categories (Figure 2). The risk of death of any cause in the low and intermediate risk groups in the validation cohort was 0.51 % and 0.58% respectively compared to 2% in the high-risk group (*p* value 0.02).

When we included symptomatic patients only, there was no significant difference in the discriminative performance of the score with an area under

the ROC curve of 0.67 in both the derivation (95% CI: 0.62-0.73) and validation (95% CI: 0.62-0.71) cohorts.

DISCUSSION

This project addresses the unmet need of how a zero-calcium score can be incorporated into a clinical strategy among patients with suspected CAD so that additional testing can be averted. The clinical risk score derived in this study predicts the presence of obstructive CAD among patients who have an Agatston score = 0. The developed tool includes clinical variables that are readily available for most of the patients upon clinical assessment and calcium score quantification performance. The relationship between current smoking and the outcome of obstructive CAD in our multivariable model was not clinically plausible and thus current smoking was excluded from our tool. This paradoxical relationship could be due to issues surrounding data collection and inaccurate classification of smoking status. Younger patients who smoke but with an overall lower risk profile are more likely to be referred for coronary CTA although there was no interaction between current smoking and other variables in our model. Model specification was done a priori through surveying a group of practicing cardiologists to avoid data-driven selection of predictors and model over-fitting.[23] We used the likelihood ratios for risk classification given the low prevalence of the outcome in the derivation cohort (2%) and the limitations of the sensitivity and specificity in such case. When validated externally in a

multicenter cohort, it showed an acceptable discriminative and classification performance. This indicates both validity and transportability of the developed score. Our score appeared to be more useful in identifying the group with low probability of having obstructive CAD and thereby can be used as a tool to guide the downstream testing in this group. Prognostically, patients in the low and intermediate risk groups had a lower risk of all-cause mortality compared to those in the higher risk group when followed up for a median follow up time of two years in the validation cohort.

Coronary Artery Calcification

Coronary artery calcification has important diagnostic and prognostic implications. CAC is a marker of atherosclerotic disease and is associated with future cardiovascular events and all-cause mortality.[1-5,24,25] When added to conventional risk factors, calcium score improves the performance of prediction models for cardiovascular events and improves the reclassification of individuals' risks. Adding the Agatston score to the Framingham risk score led to significant reclassification of individuals to higher or lower risk categories.[26-29]

Clinical Utility of an Agatston Score = 0

The Agatston score = 0 has been investigated in several studies of asymptomatic and symptomatic participants.[1,2,4-6] Raggi et. al. reported very low annual coronary event rates of 0.11% for Agatston score of zero compared to 4.8% for score of 400 or more in asymptomatic patients.[5] Among 3,409 patients with Agatston score of zero in the Multi-Ethnic Study

of Atherosclerosis (MESA), only 0.4% developed any coronary event over the follow up period of 3 years; versus an event rate of 8% for those with Agatston score ≥ 300.[4] Despite the prognostic utility of zero calcium score as proven by the low cardiovascular events rates, the presence of obstructive CAD among these patients cannot be absolutely ruled out. Several earlier studies reported a prevalence of obstructive CAD in patients with zero calcium score that varied widely from 7% to 38%.[11,30-33] This is likely explained by the high-risk presentations of populations studied and technology used. Villines et. al. reported a prevalence of 3.5% of obstructive CAD among patients with an Agatston score of zero.[12] More recently, Mittal et. al. reported a lower prevalence rate of obstructive CAD in patients with zero calcium score of 1.4 % in a cohort of mostly asymptomatic patients and patients with atypical presentation.[13]

The diagnostic uncertainty of an Agatston score = 0 has limited its clinical use to rule out obstructive CAD. Our proposed clinical risk score when combined with calcium score can improve the diagnostic utility of an Agatston score = 0 by allowing it to rule out obstructive CAD with a negative predictive value of 99%. Based on the performance of this risk score, we propose a new management algorithm for work up of suspected CAD when CCTA is considered (Figure 3). For patients presenting for CCTA to rule out obstructive CAD, those with a low risk score (≤ 6), an Agatston score be performed. In those with an Agatston score = 0, the presence of obstructive CAD can be ruled out with high certainty. Theoretically, this approach will

result in lower radiation exposure, eliminate the need for contrast media, and reduce healthcare costs.

Limitations

The definition of obstructive CAD was based on the findings from CCTA, therefore false positive and false negative cases are possible. As most of CCTA studies were performed prior to the publication of the Coronary Artery Disease-Reporting and Data System (CAD-RAD), some of the included patients with typical symptoms may have had long lesions or large volume plaque with luminal stenosis <50% which could result in ischemia. For the development of our model, we used data collected retrospectively from a tertiary care center where functional testing for CAD and invasive coronary angiogram are easily accessible; this may introduce referral bias as the cohort has an over-all lower risk of obstructive CAD. Our validation dataset was a subgroup with low rates of missing values from a larger international registry. Exclusion of other centers could have affected the representation of the validation cohort. The results of this retrospective analysis are hypothesis generating and prior to clinical implementation, should be validated in a trial with a prospectively collected data.

CONCLUSION

A novel risk score was developed and when applied to patients with an Agatston score = 0 can effectively rule out obstructive CAD and eliminate the need for further testing.

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Table 1: Clinical Characteristics of Derivation and Validation Cohorts

	Derivation Cohort		Validation Cohort	
	No Obstructive CAD (N=4,791) *n* (%) *Mean/SD*	Obstructive CAD (N=112) *n* (%) *Mean/SD*	No Obstructive CAD (N=4,083) *n* (%) *Mean/SD*	Obstructive CAD (N=207) *n* (%) *Mean/SD*
Age (years)	53 ± 10.3	53 ± 10	52 ± 12	60 ± 12
Male	1993 (42)	65 (58)	1,967 (48)	111 (54)
Pre-test Probability of CAD	0.21± 0.36	0.32± 0.32	0.30 ± 0.26	0.36 ± 0.29
Body mass index (kg/m2)	29 ± 6	30 ± 5	28 ± 5	29 ± 6
Chest pain Typical Atypical/Non-cardiac	 370 (8) 2628 (55)	 22 (20) 51 (46)	 407 (10) 2151 (53)	 23 (11) 87 (54)
Shortness of breath	2,935 (61)	61 (54)	792 (19)	42 (26)
Asymptomatic	871 (18)	16 (14)	1,111 (27)	57 (25)
Family history	2,194 (46)	56 (50)	1,481 (36)	100 (49)
Hypertension	1,838 (38)	54 (48)	1,544 (38)	104 (51)
Hyperlipidemia	1,970 (41)	67 (60)	1,644 (40)	129 (63)
Current Smoking	650 (14)	15 (13)	663 (16)	32 (16)
Diabetes mellitus	432 (9)	15 (13)	299 (7)	43 (21)
Aspirin	2,010 (42)	63 (56)	700 (17)	30 (15)
Beta blockers	1,601 (33)	47 (42)	663 (16)	19 (9)
Lipid lowering agents	1408 (29)	49 (44)	587 (14)	25 (2)
Abbreviations: CAD, coronary artery disease				

Table 2: Multivariable Clinical Model for Obstructive CAD

	Beta	Standard Error	Odds Ratio	Lower CI	Upper CI
Intercept	-5.3101	0.6457	--	--	--
Age	0.00935	0.0104	1.009	0.989	1.030
Male	0.8024	0.2105	2.231	1.477	3.370
Typical chest pain	1.0549	0.2779	2.872	1.666	4.950
Hyperlipidemia	0.6276	0.2077	1.873	1.247	2.814
Hypertension	0.2091	0.2011	1.233	0.831	1.828
Family history	0.2331	0.1971	1.262	0.858	1.858
Diabetes mellitus	0.1597	0.2954	1.173	0.657	2.093
Abbreviations: CAD, coronary artery disease; CI, 95% confidence interval.					

Table 3: Obstructive CAD Score in Patients with Agatston Score=0

Variable	Scoring Point
Age (years)	
< 30	0
30-39	1
40-49	2
50-59	3
60-69	4
≥ 70	5
Male	4
Typical chest pain	5
Dyslipidemia	3
Hypertension	1
Family history of CAD	1
Diabetes mellitus	1
Clinical Probability: low risk, ≤ 6 points; intermediate risk, 7-13 points; high risk ≥ 14 points. Abbreviations: CAD, coronary artery disease	

Table 4: Operating Characteristics for Thresholds of Obstructive CAD Score

Score	Sensitivity	Specificity	PPV	NPV	PLR	NLR
0	1.00 (0.999-1.000)	0.0	0.023 (0.019-0.027)	-	1.00	--
1	1.00 (0.979-1.000)	0.002 (0.001-0.004)	0.023 (0.019-0.027)	1.000 (0.720-1.000)	1.00	--
2	0.99 (0.958-1.000)	0.010 (0.008-0.014)	0.023 (0.019-0.028)	0.980 (0.894-1.000)	1.001(0.982-1.020)	0.877(-0.953–2.699)
3	0.98 (0.948-1.000)	0.049 (0.044-0.056)	0.024 (0.019-0.028)	0.992 (0.970-1.000)	1.033(1.005-1.062)	0.358(-0.165-0.887)
4	0.96 (0.911-0.990)	0.133 (0.124-0.143)	0.025 (0.020-0.030)	0.994 (0.984-0.998)	1.112(1.068-1.157)	0.268(-0.006-0.542)
5	0.884 (0.810-0.937)	0.237(0.225-0.249)	0.026 (0.022-0.032)	0.989 (0.981-0.994)	1.158(1.073-1.242)	0.490(0.223-0.758)
6	0.866 (0.789-0.923)	0.318 (0.305-0.331)	0.029 (0.023-0.035)	0.990 (0.984-0.995)	1.269(1.168-1.371)	0.421(0.210-0.633)
7	0.786 (0.698-0.858)	0.431 (0.417-0.445)	0.031 (0.025-0.038)	0.990 (0.983-0.993)	1.381 (1.235-1.528)	0.497(0.309-0.865)
8	0.679(0.584-0.764)	0.577 (0.563-0.591)	0.036 (0.029-0.045)	0.990 (0.982-0.992)	1.605(1.380-1.829)	0.557(0.397-0.716)
9	0.563 (0.466-0.656)	0.703 (0.690-0.716)	0.042 (0.033-0.054)	0.987 (0.981-0.989)	1.895(1.555-2.235)	0.622(0.483-0.761)
10	0.473 (0.378-0.570	0.794 (0.782-0.805)	0.051(0.038-0.066)	0.985 (0.980-0.988)	2.292(1.798-2.786)	0.664(0.540-0.788)
11	0.393 (0.302-0.490)	0.865 (0.855-0.874)	0.064(0.047-0.084)	0.984 (0.980-0.987)	2.905(2.162-3.648)	0.702(0.591-0.813)
12	0.214 (0.142-0.302)	0.918(0.910-0.925)	0.057 (0.037-0.084)	0.980 (0.976-0.984)	2.606(1.591-3.620)	0.856(0.768-0.944)
13	0.143 (0.084-0.222)	0.958(0.952-0.964)	0.074 (0.043-0.117)	0.980 (0.975-0.983)	3.405(1.694-5.115)	0.894(0.8223-0.967)
14	0.116 (0.63-	0.979(0.974-	0.114 (0.062-	0.979(0.975-	5.505(2.312-8.697)	0.903(0.839-

	0.190)	0.983)	0.187)	0.983)		0.967)
15	0.063 (0.026-0.124)	0.987(0.983-0.990)	0.100 (0.041-0.195)	0.978 (0.973-0.982)	4.753(0.930-8.576)	0.950(0.902-0.998)
16	0.027 (0.006-0.076)	0.991 (0.988-0.993)	0.064 (0.013-0.175)	0.978(0.973-0.982)	2.917(0.656-6.489)	0.982(0.950-1.014)
17	0.018(0.002-0.063)	0.996 (0.993-0.997)	0.087(0.012-0.280)	0.978(0.972-0.981)	4.074(-2.143-10.291)	0.986(0.960-1.0127)
18	0.009(0.002-0.049)	1.000 (0.998-1.000)	0.333 (0.008-0.906)	0.977(0.973-0.981)	21.38(-32.921-75.6980)	0.992(0.973-1.010)
19	0.0	1.000(0.998-1.000)	-	0.977(0.973-0.981)	0.00	1.009(0.810-1.208)
NLR: Negative likelihood ratio, NPV: Negative predictive value, PLR: Positive likelihood ratio, PPV: Positive predictive value						

Table 5: Proportions of Patients Classified by Obstructive CAD Risk Score Among Patients with Agatston Score = 0 and Predictive Accuracy of the Score

Clinical Score	Derivation Cohort		Validation Cohort	
	Total Patients N (%)	Confirmed Obstructive CAD N (%)	Total Patients N (%)	Confirmed Obstructive CAD N (%)
Low risk ≤ 6	2,090 (42.63)	24 (1.15)	1,736 (40.50)	34 (1.96)
Intermediate risk 7- 13	2,699 (55.05)	75 (2.78)	2,407 (56.11)	152 (6.31)
High risk ≥ 14	114 (2.32)	13 (11.40)	147 (3.40)	19 (12.93)
Abbreviations: CAD, coronary artery disease.				

Figure 1: ROC Curve of The Model to Predict Obstructive CAD in Derivation and Validation Cohorts

Our model has an area under the ROC curve of 0.70 (CI:0.65-0.76) in the derivation cohort (**A**) and 0.69 (95% CI:0.65-0.72) in the validation cohort (**B**) which demonstrate a robust discriminative ability.

Figure 2: Plot of Obstructive CAD Score in Derivation and Validation Cohorts

The developed risk score showed a good calibration between observed and predicted risks at low and intermediate risk score categories in the derivation and validation cohorts.

Abbreviations: ROC, receiver operating characteristics; CAD, coronary artery disease

Figure 3: Proposed Algorithm for Work Up of Obstructive CAD Based on the Obstructive CAD Risk Score

The proposed algorithm provides an illustration of the use of the obstructive CAD risk score as a clinical decision tool. In patients with zero calcium score, patients with a score of ≤ 6 points; further testing may not be needed as obstructive CAD can be ruled out with high accuracy.

Abbreviations: CAD, coronary artery disease