Exercise electrocardiography for pre-test assessment of the likelihood of coronary artery disease

Exercise electrocardiography for Pre-Test Assessment of the Likelihood of Coronary Artery Disease

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ABSTRACT

Objectives. To develop a tool including exercise electrocardiography (ExECG) for patient-specific clinical likelihood estimation of patients with suspected obstructive coronary artery disease (CAD).

Methods. An ExECG-weighted clinical likelihood (ExECG-CL) model was developed in a Training cohort of patients with suspected obstructive CAD undergoing ExECG. Secondly, the ExECG-CL model was applied in a CAD Validation cohort undergoing ExECG and clinically driven invasive coronary angiography and a Prognosis Validation cohort and compared to the risk factor-weighted clinical likelihood (RF-CL) model for obstructive CAD discrimination and prognostication, respectively.

In the CAD Validation cohort, obstructive CAD was defined as >50% diameter stenosis on invasive coronary angiography. For prognosis, the endpoint was non-fatal myocardial infarction and death.

Results. The Training cohort consisted of 1,214 patients (mean age 57years, 57% males). In the CAD (N=408; mean age 55years, 53% males) and Prognosis Validation (N=3,283; mean age 57years, 57% males) cohorts, 11.8% patients had obstructive CAD and 4.4% met the endpoint. In the CAD Validation cohort, discrimination of obstructive CAD was similar between the ExECG-CL and RF-CL models: area under the receiver-operating characteristic curves 83.1% (95% confidence intervals (CI) 77.5-88.7) versus 80.7% (95%CI 74.6-86.8), p=0.14. By the ExECG-CL model, more patients had very-low (≤5%) clinical likelihood of obstructive CAD compared to the RF-CL (42.2% vs. 36.0%, p<0.01) where obstructive CAD prevalence and event risk remained low.

Conclusions. ExECG incorporated into a clinical likelihood model improves re-classification of patients to a very-low clinical likelihood group with very-low prevalence of obstructive CAD and favorable prognosis.

Keywords: coronary artery disease; chronic coronary syndrome; clinical likelihood; pre-test probability; exercise ECG.

KEY MESSAGES:

What is already known about this subject? Exercise electrocardiography (ExECG) is recommended to modify pre-test clinical likelihood estimates of patients with de novo suspicion of obstructive coronary artery disease (CAD). However, a clinically applicable tool is missing for incorporating ExECG into the estimation of clinical likelihood.

What are the new findings?

- A novel ExECG-weighted clinical likelihood (ExECG-CL) model can be used in patients with low clinical likelihood (>5-15%) where it enables both rule-out of obstructive CAD and rule-in for downstream testing.
- In low clinical likelihood (>5-15%) patients, utilization of the ExECG-CL model does not compromise patient safety.
- The ExECG-CL model improves re-classification to a very-low clinical likelihood group with preserved very-low prevalence of obstructive CAD and favorable prognosis.

How might these results change the clinical practice? If ExECG results are available in de novo chest pain patients, utilization of the ExECG-CL model could improve patient management .

ABBREVIATIONS

ExECG	Exercise electrocardiography
CAD	Coronary artery disease
RF-CL	Risk factor-weighted clinical likelihood
CACS-CL	Coronary artery calcium score-weighted clinical likelihood
ExECG-CL	Exercise electrocardiography-weighted clinical likelihood
SCOT-HEART	Scottish computed tomography of the heart

INTRODUCTION

North-American and European guidelines on stable chest pain highlight exercise electrocardiography (ExECG) in the diagnostic work-up of chest pain-patients for assessment of exercise tolerance, symptoms, arrhythmias, blood pressure response, and future risk of cardiac events.[1 2] However, based on limited diagnostic accuracy of obstructive coronary artery disease (CAD) and rule-in for downstream testing[3], European guidelines also discourage the use of ExECG in the diagnostic work-up of stable chest pain patients when other non-invasive imaging tests are available.[1]

Pre-test clinical likelihood estimation is recommended to guide referral for non-invasive testing and treatment decisions in patients with symptoms suggestive of obstructive CAD.[1 2] Classically, the estimation is based on age, sex and symptoms yielding pre-test probability models with additional clinical likelihood modification by incorporation of, e.g. cardiovascular risk factors, coronary artery calcium score and ExECG.[1 2] However, European guidelines do not provide specific recommendations on how to incorporate these likelihood modifiers in a clinical context,[1] and North-American guidelines only highlight the coronary artery calcium score to modify patient-specific clinical likelihood.[2]

Simple and clinically applicable tools for clinical likelihood estimation including risk factors and the coronary artery calcium score have been proposed.[4] The novel risk factor-weighted clinical likelihood (RF-CL) model showed improved and safe discrimination of patients with suspected obstructive CAD compared to the currently recommended basic pre-test probability models.[1 2 4-6] In addition, when incorporating a coronary artery calcium score in the RF-CL model, the coronary artery calcium score-weighted clinical likelihood (CACS-CL) model further improved diagnostic accuracy, patient re-classification and risk prediction.[4 6] In general, ExECG is commonly available whereas a coronary artery calcium score is currently not, and to date, a clinically applicable tool is missing for incorporating ExECG into the estimation of clinical likelihood of obstructive CAD despite the continued wide use in the diagnostic work-up of chest-pain patients.[2]

The aim was to develop and validate a useful tool including ExECG for patient-specific clinical likelihood estimation in symptomatic de novo chest pain patients with suspected obstructive CAD.

METHODS

Overview of study design. Based on previous experience outlining the discriminative gain of complementary risk factors and a coronary artery calcium score to a clinical likelihood estimation at the initial patient encounter of de novo chest pain-patients, we developed and calibrated an ExECG-weighted clinical likelihood (ExECG-CL) model to estimate the prevalence of obstructive CAD utilizing a Training cohort.[7] The ExECG-CL model discrimination and calibration was subsequently validated in an external CAD Validation cohort using invasive coronary angiography as reference for obstructive CAD.[8] Finally, the developed model was validated for prognosis in a Prognosis Validation cohort.[7] For both discrimination of obstructive CAD and prognostication, the ExECG-CL model was compared with the RF-CL model which did not utilize additional ExECG results to modify the clinical likelihood estimation.

Training cohort. The Training cohort was identified from the Scottish computed tomography of the heart (SCOT-HEART) study.[7] In short, all patients underwent routine clinical assessment including, if deemed appropriate, symptom-limited ExECG testing (performed in 3.283 (79%) patients). After recruitment including amendment to standard care, patients were randomly allocated to either 1) standard care alone (Standard care arm) or 2) standard care with additional coronary computed tomography angiography (CTA) (Standard care+CTA arm). The CAD Training cohort was restricted to patients allocated to the Standard care+CTA arm with ExECG and CTA data available (n=1,412).

In the Training cohort, obstructive CAD was defined as >50% diameter stenosis on coronary CTA.

CAD Validation cohort. The CAD Validation cohort included prospectively enrolled patients referred for out-patient cardiac evaluation due to symptoms of obstructive CAD from the Netherlands (n=408).[8] All patients were without previously documented CAD and underwent ExECG, coronary CTA and clinically driven invasive coronary angiography.

In the CAD Validation cohort, obstructive CAD was defined as invasive coronary angiography with >50% diameter stenosis. In a secondary sensitivity analysis, obstructive CAD was defined as >50% diameter stenosis by CTA.

Prognosis Validation cohort. Investigation of the prognostic value of the RF-CL and ExECG-CL models was performed in the SCOT-HEART cohort using all patients who had undergone ExECG from both the Standard care and Standard care+CTA arms (Prognosis Validation cohort, n=3,283).[7] The primary end-point was non-fatal myocardial infarction and death.

A sensitivity analysis was performed stratifying patients according to whether patients were included in the Training cohort and hence used for the development of the ExECG-CL model against obstructive CAD.

Exercise ECG. In all patients in the Training, CAD and Prognosis Validation cohorts, ExECGs were performed according to the standard Bruce protocol. Criteria for myocardial ischemia and hence an abnormal ExECG included horizontal or down-sloping ST depression or elevation >0.1 mSv during or after exercise, or typical, increasing angina during exercise. The ExECGs was considered inconclusive if the test was discontinued without evidence of myocardial ischemia before the 85% target heart rate was reached. If none of the above-mentioned scenarios occurred, the ExECG was considered normal.

Calculation of clinical likelihood models. The RF-CL model was calculated from sex, age and type of chest pain with additionally implementation of the number of risk factors ranging from 0 to 5.[4] The ExECG-CL model incorporated ExECG results into the RF-CL model. Variables were defined as reported in the **Supplemental material**, "*Definition of variables*". Both models were arbitrarily divided into risk groups of very-low (≤5%), low (>5-15%) and moderate-high (>15%) clinical likelihood of obstructive CAD.

Ethical approval. The study was approved by the Ethical Committee boards of the University of Edinburgh and the Erasmus University Rotterdam.[7 8]

Patient and public involvement. Patients and the public were not involved in the study design or study conduction, choice of outcome measures or recruitment of the study.

Statistical analyses. The ExECG-CL model was developed in the Training cohort using coronary CTA as reference of obstructive CAD (**Supplemental material,** "*Development of Exercise ECG-weighted clinical likelihood*"). As the original RF-CL was calibrated to invasive coronary angiography as reference standard for obstructive CAD, step 1 included re-scaling the RF-CL to the CTA positive rate by training a logistic regression model with the logit transformed RF-CL score as the only input. Step 2 included a second logistic regression utilizing the logit transformed re-scaled RF-CL score and the ExECG results categorized as normal, inconclusive or abnormal. Step 3 combined Ex-ECG coefficients from step 2 with the original RF-CL model calibrated against invasive coronary angiography for development of the ExECG-CL model (**Supplemental Table 1**). Hence, the final Ex-ECG-CL model predicts the prevalence of obstructive CAD with a reference standard of invasive coronary angiography.

Continuous variables are expressed as mean with standard deviations (SD), and dichotomous or categorical variables are reported as n (%). External validation of the ExECG-CL was performed in the validation cohort using invasive coronary angiography as reference standard of obstructive CAD. First, calibration plots of the mean predicted probability and the mean observed prevalence of obstructive CAD with flexible calibration (Loess bandwidth 0.8) were evaluated. Perfect predictions should be on the ideal line in the calibration plot, statistically described with an intercept alpha of 0 ("calibration-in-the-large") and slope beta of 1 ("calibration slope"). Secondly, discrimination was assessed using the area under the receiver operating characteristic curve (AUC) and compared by the DeLong algorithm. Net re-classification improvement was investigated. Additionally, diagnostic performance was evaluated by sensitivity, specificity, positive and negative predictive values using a ≤5% CL cut-off and compared using McNemar´s test and a weighted generalized score.

For time-to-event analyses, the primary end-point was non-fatal myocardial infarction and death. Unadjusted hazard ratios were calculated, Kaplan-Meier curves computed for visualization of mortality, and time-dependent AUC curves compared.[9]

RESULTS

Baseline characteristics of the Training and CAD Validation cohorts are shown in **Table 1**. The Training cohort consisted of 1,214 patients with mean age of 57 years of whom 57% were males. The CAD validation cohort consisted of 408 patients with mean age of 55 years of whom 53% were males. In the Training cohort by coronary CTA, obstructive CAD was identified in 353/1,412 (25.0%) patients. In the CAD Validation cohort, obstructive CAD was identified by coronary CTA in 128/408 (31.4%) patients and by invasive coronary angiography in 48/408 (11.8%) patients.

Development of the ExECG-CL model in the Training cohort. Patient distribution according to the ExECG results stratified by RF-CL categories is shown for the Training cohort in **Table 2** and **Supplemental Figure 1.** Overall, 536 (38.0%), 471 (33.4%) and 405 (28.7%) patients were identified using the RF-CL model as having very-low, low and moderate-high clinical likelihood of obstructive CAD, respectively. ExECG found normal, inconclusive and abnormal test results in 921 (65.2%), 255 (18.1%) and 236 (16.7%) patients, respectively. The prevalence of normal ExECGs decreased with increasing RF-CL, whereas the prevalence of inconclusive and abnormal ExECGs increased. In addition, the prevalence of obstructive CAD was lower in patients having a normal ExECG compared to patients having an abnormal ExECG.

In the Training cohort, median ExECG-CL was 5.4% [IQR: 2.0-17.0%] (**Figure 1** and **Supplemental Table 1**). Overall, the ExECG-CL model showed higher discrimination of obstructive CAD defined by coronary CTA compared to the ExECG results alone and the RF-CL model; AUC ExECG-CL 80.2 (77.4-82.7) vs. ExECG 69.5 (66.4-72.5), $p<0.001$ and RF-CL 78.3 (75.6-81.0), $p<0.001$, respectively.

Validation of the ExECG-CL model. In the CAD Validation cohort, median ExECG-CL was 6.6% [IQR: 2.7-15.3%]. **Supplemental Figure 1** shows patient distribution and obstructive CAD prevalence using CTA and invasive coronary angiography as reference standards stratified by ExECG results in the CAD Validation cohort.

Using CTA as reference of obstructive CAD in the CAD Validation cohort, the ExECG-CL model had similar discrimination as the RF-CL model (AUC ExECG-CL 76.8 (95% CI 71.7-81.8) vs. RF-CL 75.4 (95% CI 70.4-80.5), p=0.25), whereas discrimination was higher compared to the ExECG results alone (95% CI AUC 61.5 (55.8-67.2), p<0.001).

Using invasive coronary angiography as reference standard of obstructive CAD in the CAD Validation cohort, the predicted likelihood of obstructive CAD showed excellent calibration against the observed prevalence for both the ExECG-CL and the RF-CL models, respectively (RF-CL: calibration in the large=0.05, slope=1.2; ExECG-CL: calibration in the large=0.03, slope=1.09) (**Figure 2A**). Overall diagnostic performance of the ExECG-CL model was similar to that of the RF-CL model in the CAD Validation cohort (AUC 80.7% (95% CI 74.6-86.8) vs. 83.1% (95% CI 77.5-88.7), p=0.14) (**Figure 2B**). However, more patients were categorized with very-low clinical likelihood (≤5%) of obstructive CAD when the ExECG-CL model was applied compared with the RF-CL alone (42.2% vs. 36.0%, p<0.01), and the prevalence of obstructive CAD in down-classified patients remained low **(Figure 2C, Supplemental table 2**). Additionally, fewer patients had low clinical likelihood (>5-15%) by the ExECG-CL model (32.1% vs. 39.7%, p<0.01). Compared to the RF-CL, the ExECG-CL model showed higher specificity (46.9% (95% CI 41.7-52.2) vs. 40.0% (95% CI 34.9-45.3), p=0.01) while sensitivities, NPVs and PPVs were similar between the models (**Figure 2D**).

The net reclassification improvement for the ExECG-CL model was 21.7% (95% CI 3.7-39.7%, p=0.01) (**Supplemental Table 2**). In particular, the ExECG-CL model improved re-classification of patients to a very-low clinical likelihood category compared with the RF-CL model. Compared to the RF-CL model, the ExECG-CL model was able to down-classify patients with >5-8% clinical likelihood to ≤5% clinical likelihood of obstructive CAD if showing a normal ExECG result and was able to up-classify patients with >8-15% clinical likelihood of obstructive CAD to >15% clinical likelihood of obstructive CAD

if showing an abnormal test result (**Figure 1**). An inconclusive ExECG results had no re-classification potential.

RF-CL, ExECG-CL and prognosis. The Prognosis Validation cohort consisted of 3,283 patients with mean age of 57 years of whom 57% were males (**Supplemental table 3**). During a follow-up of up to 7.2 (4.7 [4.0-5.7]) years in the Prognosis Validation cohort, myocardial infarction and death occurred in 144/3,283 (4.4%) patients. Overall, event rates increased with increasing RF-CL and ExECG-CL (**Figure 3**), with declining event rates over time (**Supplemental Figure 3**). No event rate difference was observed for patients categorized by the RF-CL compared to the ExECG-CL; very-low (0.2% (0.2-0.6) vs. 0.2% (0.3-0.6), p=0.36), low (0.7% (0.6-1.1) vs. 0.4% (0.7-1.4), p=0.21) and moderate-high (1.9% (1.5-2.4) vs. 1.9% (1.5-2.4), p=0.44 (**Supplemental table 4**).

In a sensitivity analysis comparing patients used for ExECG-CL model development (Training cohort, n=1,412) to those excluded from the Training cohort (Non-training cohort, n=1,871), baseline characteristics were similar (**Supplemental Table 3**). Additionally, the ability of the ExECG-CL model to prognosticate remained good and similar to the RF-CL model (absolute 5-year risk 2.1 vs. 2.4% for the RF-CL and ExECG-CL models, respectively, p=0.41 (**Supplemental Figure 4)).**

DISCUSSION

This study introduces a simple tool based on ExECG for patient-specific clinical likelihood estimation in de novo chest pain-patients with suspected obstructive CAD. The model can be used in patients with low clinical likelihood (>5-15%) where it enables both rule-out of obstructive CAD and rule-in for downstream testing. Importantly, the ExECG-CL model improves re-classification to a very-low clinical likelihood group with preserved low prevalence of obstructive CAD compared to the RF-CL model. Additionally, prognosis in this subset of patients remains good.

Clinical likelihood and chronic coronary syndrome. Recognized as a gap in evidence by the 2019 European Society of Cardiology guidelines on chronic coronary syndrome[1], the RF-CL model was developed as a tabulated, simple and clinically useful tool for improved prediction of obstructive CAD in de novo chest pain patients.[4] Furthermore, the implementation of the coronary artery calcium score (i.e., the CACS-CL model) was equivalently to ExECG testing consistent with the suggestion that clinical likelihood is modified to either increase or decrease patient-specific probability with later North-American endorsement.[2]

Importantly, clinical likelihood refinement by implementation of risk factors and a coronary artery calcium score specifically identifies more patients at very-low clinical likelihood of obstructive CAD[1 4 5 10] where downstream testing can be deferred (**Figure 2**).[1 2] Despite a less pronounced down-re-classification by additional ExECG compared to a coronary artery calcium score[1 4 5 10], clinical likelihood refinement is possible beyond risk factor assessment alone (**Figure 2C**, **Supplemental Table 2**). As patients with >5-15% clinical likelihood have ambiguous recommendations for downstream testing[1 2], a reduced proportion of patients within this "test/no test" gray zone underlines the potential of using ExECG results for clinical likelihood modification.

Originally, both the RF-CL, CACS-CL and now the ExECG-CL were validated against a reference standard of obstructive CAD by diameter stenosis on invasive coronary angiography.[4] Overall, the calibration of clinical likelihood models is impacted by the chosen reference standard of obstructive CAD[4 11] and as 1) pre-test clinical likelihood estimations are utilized for assessment of post-test disease probability after advanced non-invasive diagnostic testing[3], and 2) abnormal test results guide potential revascularization based on stenosis severity on invasive coronary angiography, clinical likelihood models should be validated and calibrated against invasive coronary angiography.[4 8] Previous studies report very good calibration of the RF-CL model[4 5 12] which is validated in the present cohorts as novel findings. Importantly, the excellent calibration of the RF-CL model persisted after inclusion of ExECG (**Figure 2B**).

Previously, ExECG has been suggested to stratify patients with obstructive CAD.[13-16] However, analyses are limited by either retrospective inclusion, reference standards of either prognosis alone or coronary CTA, or inclusion of patients with known CAD. Importantly, no study to our knowledge has

investigated how ExECG modifies the clinical likelihood of obstructive CAD and impacts diagnostic management when applied to a risk factor-based clinical assessment.

Prognosis in chronic coronary syndrome. Globally, the ExECG remains a frequently applied test for discrimination of obstructive CAD.[2] Overall, the diagnostic accuracy of obstructive CAD using ExECG is lower than imaging-based modalities[17-21] but the ability to prognosticate is similar.[13 22]

In our study, we did not find risk stratification by the ExECG-CL model superior to the RF-CL model and did not show improved stratification after inclusion of ExECG to the RF-CL model. However, the ExECG-CL model found patients with very-low clinical likelihood by the ExECG-CL to have a 5-year absolute risk <2.5% of myocardial infarction and death (**Figure 3**), and the improved down-reclassification of the ExECG-CL model compared to the RF-CL model additionally is safe.

Clinical implications. By calibration against a reference standard of obstructive CAD, both the RF-CL and ExECG-CL models potentially defer testing in patients with non-obstructive CAD which then remains unrecognized. In contrast, the coronary artery calcium score is a strong predictor of CAD in general[4 23] where guideline-directed medical therapy potentially improves prognosis in patients with both non-obstructive and obstructive lesions.[19 24] Compared to previous studies highlighting a potentially superior re-classification and risk stratification, a coronary artery calcium score-driven approach for clinical likelihood modification seems preferable over an ExECG strategy.[17] However, randomized coronary artery calcium score-driven management trials are limited in patients with suspected CAD[17 25], and importantly, the ExECG-CL model *did* improve re-classification of patients to a very-low CL group with low prevalence of obstructive CAD and favorable prognosis compared to the RF-CL model (**Figure 2c**, **Figure 3**).

Limitations. Patients in the CAD Validation cohort were referred for clinically indicated invasive coronary angiography which could induce selection bias. In addition, patients with a very-low clinical likelihood are not consistently referred for diagnostic testing and patients with severe kidney disease or severe obesity may be under-represented as all patients had to be eligible for coronary CTA. In addition, most patients were

Caucasians, which might limit the extrapolation to more multiethnic populations. Finally, validation of CAD discrimination was only performed in a single external cohort including 408 patients, which limits the certainties of results. However, to the best of our knowledge, the studies included in the present analysis represent the only contemporary studies with ExECG and angiography systematically performed in all patients.

Conclusions. ExECG incorporated into a clinical likelihood model improves re-classification of patients to a very-low clinical likelihood group with low prevalence of obstructive CAD and favorable prognosis.

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Data availability statement. Data was shared by D. E. Newby and K. Nieman for the present analysis.

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FIGURE LEGENDS

Figure 1. Clinical likelihood of obstructive coronary artery disease (CAD) based on age, sex, type of symptoms and number of risk factors (A) and ExECG testing. Values are the estimates for patients 35, 45, 55, 65, and 75 years of age. Typical chest pain was defined as: 1) constricting discomfort in the chest, neck, jaw, shoulder, or arm; which was 2) provoked by exertion or emotional stress; and 3) relieved by rest or nitroglycerine within 5 min. Atypical chest pain was defined as 2 of the previously mentioned criteria. If 1 or none of the criteria were present, the symptoms were categorized as nonanginal chest pain. Dyspnoea was defined as exertional dyspnoea as the primary symptom.
Abbreviations: CAD=coronary artery disease; CTA=computed tomography angiography; RF-CL: Risk Factor-weighted Clinical Likelihood; ECG=electrocardiogram.

Figure 2. Diagnostic performance of the RF-CL and ExECG-CL models against obstructive CAD by ICA in the CAD validation cohort (n=408). (A) The calibration plots show good calibration of both models. (B) Receiver-operating characteristic curves show similar and good discrimination by both models. (C) The distribution of patients according to clinical likelihood cut-offs and the corresponding prevalence of obstructive CAD illustrate the reclassification ability of the ExECG model. (D) The diagnostic accuracy evaluated with sensitivity, specificity, and positive and negative predictive values with a clinical likelihood cut-off of 5% demonstrate high sensitivities and negative predictive values of both models.
For Figure 2C, bold numbers are numbers of patients with obstructive CAD in relation to number of patients classified within a specific clinical likelihood category.
Abbreviations: As in Figure 1 + CI=confidence interval.

Figure 3. Kaplan-Maier curves against the primary end-point of non-fatal myocardial infarction and death stratified by RF-CL groups (A), ExECG results (B) and ExECG-CL groups (C).
Abbreviations: as in Figure 1.

TABLES

Table 1: Baseline characteristics for study cohort		
	Scot-Heart N=1,412	**Nieman et al. N=408**
Characteristics		
Male	800 (56.7)	215 (52.7)
Age		
Mean age (years)	57.4 ± 9.3	55.3 ± 9.8
<50	294 (20.8)	104 (25.5)
50-60	486 (34.4)	177 (43.4)
60-70	491 (34.8)	93 (22.8)
≥70	106 (7.5)	29 (7.1)
Risk factors		
Family history of early CAD	617 (43.7)	187 (45.8)
Smoking history	701 (49.6)	236 (57.8)
Dyslipidemia	862 (61.0)	246 (60.3)
Hypertension	461 (32.6)	195 (47.8)
Diabetes	12 (0.8)	52 (12.7)
Cardiac symptoms at referral		
Typical chest pain	515 (36.5)	130 (31.9)
Atypical chest pain	346 (24.5)	215 (52.7)
Non-specific chest pain	551 (39.0)	63 (15.4)
Coronary computed tomography anagiography		
Non-obstructive CAD	1,059 (75.0)	280 (68.6)
Obstructive CAD	353 (25.0)	128 (31.4)
Invasive coronary angiography		
No or non-obstructive CAD	NA	360 (88.2)
Obstructive CAD	NA	48 (11.8)

Table 1: Baseline characteristics for the Training and CAD validation cohorts.

Values are n (%) or mean +/- SD.

CAD=coronary artery disease.

Table 2. Exercise ECG results stratified by RF-CL categories and prevalences of obstructive CAD according to exercise ECG result and RF-CL category in the Training cohort.					
	Likelihood of CAD	Total	Very low RF-CL ≤ 5%	Low RF-CL 5-15%	Moderate to high RF-CL >15%
Exercise ECG results (n)	Normal	921 (65.2)	464 (85.6)	309 (65.6)	148 (36.5)
	Inconclusive	225 (18.1)	56 (10.5)	99 (21.0)	100 (24.7)
	Abnormal	236 (16.7)	16 (3.0)	63 (13.4)	157 8.8)
Prevalence of obstructive CAD according to exercise ECG results and RF-CL tabulation					
Exercise ECG results	Normal	139 (15.1)	26 (5.6)	57 (18.5)	56 (37.8)
	Inconclusive	77 (30.2)	9 (16.1)	19 (19.2)	49 (49.0)
	Abnormal	137 (58.1)	3 (18.8)	22 (34.9)	112 (71.3)

Table 2. Exercise ECG results stratified by RF-CL categories and prevalences of obstructive CAD according to exercise ECG result and RF-CL category in the Training cohort.

Values are n (%).

Abbreviations: CAD=coronary artery disease; RF-CL=risk factor-weighted clinical likelihood; ECG=electrocardiography