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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 76, NO. 21, 2020

PUBLISHED BY ELSEVIER

ORIGINAL INVESTIGATIONS

Incorporating Coronary Calcification Into Pre-Test Assessment of the Likelihood of Coronary Artery Disease

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ABSTRACT

BACKGROUND The prevalence of obstructive coronary artery disease (CAD) in symptomatic patients referred for diagnostic testing has declined, warranting optimization of individualized diagnostic strategies.

OBJECTIVES This study sought to present a simple, clinically applicable tool enabling estimation of the likelihood of obstructive CAD by combining a pre-test probability (PTP) model (Diamond-Forrester approach using sex, age, and symptoms) with clinical risk factors and coronary artery calcium score (CACS).

METHODS The new tool was developed in a cohort of symptomatic patients (n = 41,177) referred for diagnostic testing. The risk factor–weighted clinical likelihood (RF-CL) was calculated through PTP and risk factors, while the CACS–weighted clinical likelihood (CACS-CL) added CACS. The 2 calculation models were validated in European and North American cohorts (n = 15,411) and compared with a recently updated PTP table.

RESULTS The RF-CL and CACS-CL models predicted the prevalence of obstructive CAD more accurately in the validation cohorts than the PTP model, and markedly increased the area under the receiver-operating characteristic curves of obstructive CAD: for the PTP model, 72 (95% confidence intervals [CI]: 71 to 74); for the RF-CL model, 75 (95% CI: 74 to 76); and for the CACS-CL model, 85 (95% CI: 84 to 86). In total, 38% of the patients in the RF-CL group and 54% in the CACS-CL group were categorized as having a low clinical likelihood of CAD, as compared with 11% with the PTP model.

CONCLUSIONS A simple risk factor and CACS-CL tool enables improved prediction and discrimination of patients with suspected obstructive CAD. The tool empowers reclassification of patients to low likelihood of CAD, who need no further testing. (J Am Coll Cardiol 2020;76:2421–32) © 2020 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

Manuscript received July 1, 2020; revised manuscript received September 16, 2020, accepted September 18, 2020.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2020.09.585

ABBREVIATIONS AND ACRONYMS

AUC = area under the receiver-operating characteristic curve

CACS = coronary artery calcium score

CACS-CL = coronary artery calcium score-weighted clinical likelihood

CAD = coronary artery disease

CI = confidence interval

CTA = computed tomography angiography

ESC = European Society of Cardiology

ICA = invasive coronary angiogram

NRI = net reclassification improvement

PTP = pre-test probability

RF-CL = risk factor-weighted clinical likelihood

Estimation of disease probability in patients with "stable" symptoms suggestive of obstructive coronary artery disease (CAD), chronic coronary syndromes, is a common challenge in clinical medicine. Approximately 1% of all contacts to general practitioners are related to chest discomfort, and consequently, millions of diagnostic tests are performed worldwide (1).

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Both European and American guidelines have traditionally recommended estimating the pre-test probability (PTP) of CAD based on the classic Diamond-Forrester approach using sex, age, and type of chest complaints (2,3). The information is used to guide diagnostic testing and clinical management. Recent studies have shown that the prevalence of obstructive CAD is lower than previous PTP models have indicated and reported a low diagnostic yield of currently utilized diagnostic methods (4-6). Hence, a more personalized method for estimation of disease probability is needed.

The European Society of Cardiology (ESC) has recently suggested a novel concept of clinical likelihood of CAD as a more comprehensive assessment of CAD probability (2). The estimation of clinical likelihood can be derived from PTP models incorporating the cardiovascular risk factors and computed tomography-derived coronary artery calcium scores (CACS) associated with obstructive CAD. However, a clinically feasible and validated tool to estimate clinical likelihood of CAD was recognized as a "gap in evidence" in the recent ESC guidelines on the diagnosis and management of chronic coronary syndromes (2).

The aim of this study was to develop and validate a simple clinically useful tool for individual estimation of the likelihood of obstructive CAD in symptomatic patients with suspected disease.

METHODS

OVERVIEW OF STUDY DESIGN. This study used 4 large cohorts of patients with symptoms suggestive of obstructive CAD referred for noninvasive testing using coronary computed tomography angiography (CTA). Patients were all without previously diagnosed CAD. We developed the models to estimate clinical likelihood of CAD utilizing a large training cohort, and the models were subsequently validated in 3 different patient cohorts and compared with the PTP model based on the Diamond-Forrester approach (sex, age, and symptoms) recommended by the 2019 ESC guidelines.

TRAINING COHORT. The training cohort included patients (n = 41,177), who underwent first-time coronary CTA from 2008 to 2017 in all 13 hospitals in the Western part of Denmark (uptake area 3.3 million; 55% of the total Danish population) (7). All patients were registered in the mandatory regional Danish population-based clinical database, the Western Denmark Heart Registry (WDHR). The Danish Data Protection Agency approved the study. The information is based on the clinical evaluation and includes data regarding cardiac risk factors and symptoms at the time of referral for coronary CTA. The WDHR also contains information on the results of coronary CTA and all subsequent invasive coronary angiograms (ICAs).

VALIDATION COHORTS. Temporal validation was performed utilizing WDHR data on patients, who underwent first-time coronary CTA from January 2018 to August 2019 (n = 9,383).

The model was also validated in the Dan-NICAD (Danish study of Non-Invasive testing in Coronary Artery Disease), which was a 2-center, cohort trial including consecutive patients referred for coronary CTA (n = 1,675) from 2014 to 2016 (8,9). All patients underwent a structured interview to assess cardiac risk factors and symptoms before diagnostic testing. Patients with suspected obstructive CAD at coronary CTA (n = 392) also underwent subsequent ICAs with conditional fractional flow reserve. The Danish Data Protection Agency and the Central Denmark Regional Committee on Health Research Ethics approved the study.

Finally, the model was validated in the PROMISE (Prospective Multi-center Imaging Study for Evaluation of Chest Pain) study (10,11). This randomized trial was performed in North America in 193 centers from 2010 to 2013 and included symptomatic low- or intermediate-risk outpatients without previously diagnosed CAD whose physicians deemed that nonurgent, noninvasive cardiovascular testing was necessary for the evaluation of suspected CAD. The study protocol was approved by the local or central Institutional Review Board at each enrolling site. The validation cohort for this study included only those randomized to and undergoing coronary CTA with interpretable results (n = 4,403). Subsequent ICA was performed if deemed necessary by local physicians.

DEFINITIONS OF VARIABLES. The basic variables included sex, age, and type of symptoms at referral. Typical chest pain was defined as constricting

discomfort in the chest or neck, jaw, shoulder, or arm provoked by exertion or emotional stress and relieved by rest or nitroglycerine. Atypical chest pain was defined as 2 of the previously mentioned criteria. If 1 or none of the criteria were present, chest pain symptoms were categorized as nonanginal chest pain. Dyspnea was defined as having exertional dyspnea as the primary symptom.

The risk factors included in the analysis were family history of CAD, smoking, dyslipidemia, hypertension, diabetes, reduced glomerular filtration rate, and increased body mass index. Smoking was defined as currently smoking or having a history of smoking. The local physicians or when patients received medical treatment for dyslipidemia, hypertension, and diabetes defined these conditions. Family history of CAD was defined as 1 or more close relatives with early signs of CAD (defined in the WDHR and Dan-NICAD trial as men <55 years of age and women <65 years of age, and in PROMISE trial as men and women <55 years of age).

REFERENCE OF STANDARD FOR OBSTRUCTIVE CAD. The reference standard for obstructive CAD in the WDHR training and validation cohorts was defined as ≥50% diameter stenosis on ICA performed within 120 days after coronary CTA.

In the Dan-NICAD and PROMISE trial validation cohorts, obstructive CAD was defined according to the most clinically relevant definition of obstructive CAD based on the trial tests. In the Dan-NICAD trial cohort, all patients with a suspected 50% diameter stenosis on CTA also underwent ICA. Obstructive CAD was defined based on the ICA as fractional flow reserve <0.80 or a visual diameter stenosis ≥90%. In the PROMISE trial cohort, ICA was not performed in all patients with suspected stenosis on the site reading of the CTA. Hence, obstructive CAD was defined as a ≥50% diameter stenosis on ICA or core lab analysis of CTA if ICA was not performed.

STATISTICAL ANALYSIS. The new clinical likelihood models were developed according to previous recommendations (12,13). We used regression analysis and the advanced machine learning software XGBoosting, Python module version 0.90 (XGBoost, University of Washington, Seattle, Washington). The models were then simplified using statistical arguments as presented in the Supplemental Appendix (Supplemental Tables 1 and 2, Supplemental Figures 1 and 2). The clinical likelihood models were developed in the training cohort and subsequently validated. Plugin software to commercially available statistical software packages was developed for calculating the new models (Supplemental Table 3).

The clinical likelihood modes were compared with the PTP model based on the Diamond-Forrester approach, including sex, age, and type of symptoms, was calculated according to the updated table based model recommended in 2019 by the ESC (2). In addition, the clinical likelihood modes were compared with the 3 more advanced CAD consortium models that require online calculation (14). The 3 CAD consortium models included: 1) a "basic model," which is another recalibration of the Diamond-Forrester approach; 2) a "clinical model," which expands the basic model with cardiovascular risk factors including diabetes, hypertension, dyslipidemia, and smoking; and 3) finally, a "clinical+CACS model," which included the CACS into the clinical model.

Discrimination was assessed using the area under the receiver operating characteristic curve (AUC) and the net reclassification improvement (NRI). AUCs were compared using the DeLong algorithm. Sensitivity analysis was performed to estimate the impact of diagnostic criteria for obstructive CAD. Furthermore, sensitivity analysis was performed on age and sex strata and on Caucasian and non-Caucasian patients in the PROMISE trial.

RESULTS

Baseline characteristics and diagnostic test results for the training and validation cohorts are shown in **Table 1**, and data stratified for patients with and without obstructive stenosis in each of the 4 cohorts in Supplemental Table 4.

Obstructive CAD was diagnosed in 8.8% and 10.1% of the patients in the training and validation cohorts, respectively. These values were lower than the prevalence (15.4%) predicted using the PTP tables based on sex, age, and symptoms. The number of patients and the observed prevalence of obstructive CAD for subgroups of patients in the 4 separate cohorts are shown in Supplemental Figure 3.

RISK FACTOR–WEIGHTED MODEL FOR CLINICAL LIKELIHOOD. We identified the risk factors having an impact on the observed prevalence of obstructive CAD using different machine learning models (Supplemental Figure 1). By hierarchical inclusion of the various risk factors to the basic model based on age, sex, and symptoms, only family history, smoking, dyslipidemia, hypertension, and diabetes increased the model discrimination (Supplemental Tables 1 and 2). The impact of each individual risk factor on the observed prevalence of obstructive CAD was incremental and of similar magnitude such that an increasing number of risk factors increased the observed prevalence of obstructive CAD across sex,

TABLE 1 Patient Demographics and Diagnostic Test Results

	Training Cohort (n = 41,177)	Validation Cohorts (n = 15,411)
Characteristics		
Male	18,771 (45.6)	7,522 (48.8)
Age	57.0 ± 11.4	59.2 ± 10.6
<40 yrs	2,882 (7.0)	552 (3.6)
40–<50 yrs	8,159 (19.8)	2,165 (14.0)
50–<60 yrs	12,893 (31.3)	5,367 (34.8)
60–<70 yrs	11,958 (29.0)	4,878 (31.7)
≥70 yrs	5,285 (12.8)	2,448 (15.9)
Body mass index, kg/m^2	26.7 ± 4.4	28.2 ± 5.3
Risk factors and symptoms		
Family history of early CAD	16,459 (40.0)	5,703 (37.0)
Smoking		
Never	16,200 (39.4)	6,402 (41.5)
Former	13,376 (32.5)	4,978 (32.3)
Active	8,617 (20.9)	2,730 (17.7)
Dyslipidemia	12,126 (29.5)	6,119 (39.7)
Hypertension	14,481 (35.2)	6,906 (44.8)
Diabetes	2,728 (6.6)	1,815 (11.8)
eGFR, ml/min/1.73 m^2*	87 (77–99)	85.4 ± 16.5
Cardiac symptoms at referral		
Typical chest pain	4,946 (12.0)	2,220 (14.4)
Atypical chest pain	19,619 (47.7)	8,756 (56.8)
Nonspecific chest pain	13,503 (32.8)	3,152 (20.5)
Dyspnea	3,109 (7.6)	1,282 (8.3)
Coronary artery calcium score	0 (0–69)	8 (0–119)
0	19,722 (47.9)	6,072 (39.4)
1–9	2,933 (7.1)	1,260 (8.2)
10–99	7,478 (18.2)	3,150 (20.4)
100–399	5,113 (12.4)	2,256 (14.6)
400–999	19,724 (8)	1,133 (7.4)
≥1,000	1,052 (2.6)	548 (3.6)
Disease severity by coronary computed tomography angiography		
Nonobstructive CAD	32,651 (79.3)	11,931 (77.4)
Suspected obstructive CAD†	10,015 (20.7)	3,479 (22.6)
Invasive coronary angiography		
Performed	9,230 (16.3)	2,291 (14.9)
Obstructive CAD†	3,222 (7.8)	1,569 (10.2)
Revascularization	2,460 (6.0)	1,068 (6.9)
Percutaneous coronary intervention	1,903 (4.7)	823 (5.3)
Coronary artery bypass grafting	557 (1.4)	234 (1.5)

Values are n (%), mean ± SD, or median (interquartile range). *eGFR is calculated from the Chronic Kidney Disease Epidemiology Collaboration creatinine equation. †See the definition of obstructive CAD in the Methods section.

CAD = coronary artery disease; eGFR = estimated glomerular filtration rate.

age, and symptom groups (Supplemental Figures 4 and 5). In patients with 2 to 3 risk factors, the prevalence of obstructive CAD was close to the PTP model based on only sex, age, and symptoms. Conversely, in the patients with 0 or 1 risk factor, the prevalence of CAD was lower, and in patients with 4 or 5 risk factors, the prevalence was higher than estimated by the PTP model (**Figure 1**).

Using the risk factor categories (0 to 1, 2 to 3, or 4 to 5) in a logistic regression model with sex, age, and symptoms, we developed a simple risk factor-weighted clinical likelihood (RF-CL) model (**Central Illustration**, Supplemental Table 3). The distribution of patients and the prevalence of CAD for the PTP and the RF-CL models in the training and validation cohorts are shown in **Figure 2**. The calibration of the RF-CL model was superior to the PTP model (Supplemental Figures 6 and 7).

The diagnostic performance of the RF-CL model was similar to the advanced machine learning model in the training cohort (Supplemental Table 1). The AUC of the RF-CL model in the validation cohort was 74.9 (95% confidence interval [CI]: 73.7 to 76.1), which was higher than AUC in the PTP model (72.3; 95% CI: 71.0 to 73.6) (**Figure 3**).

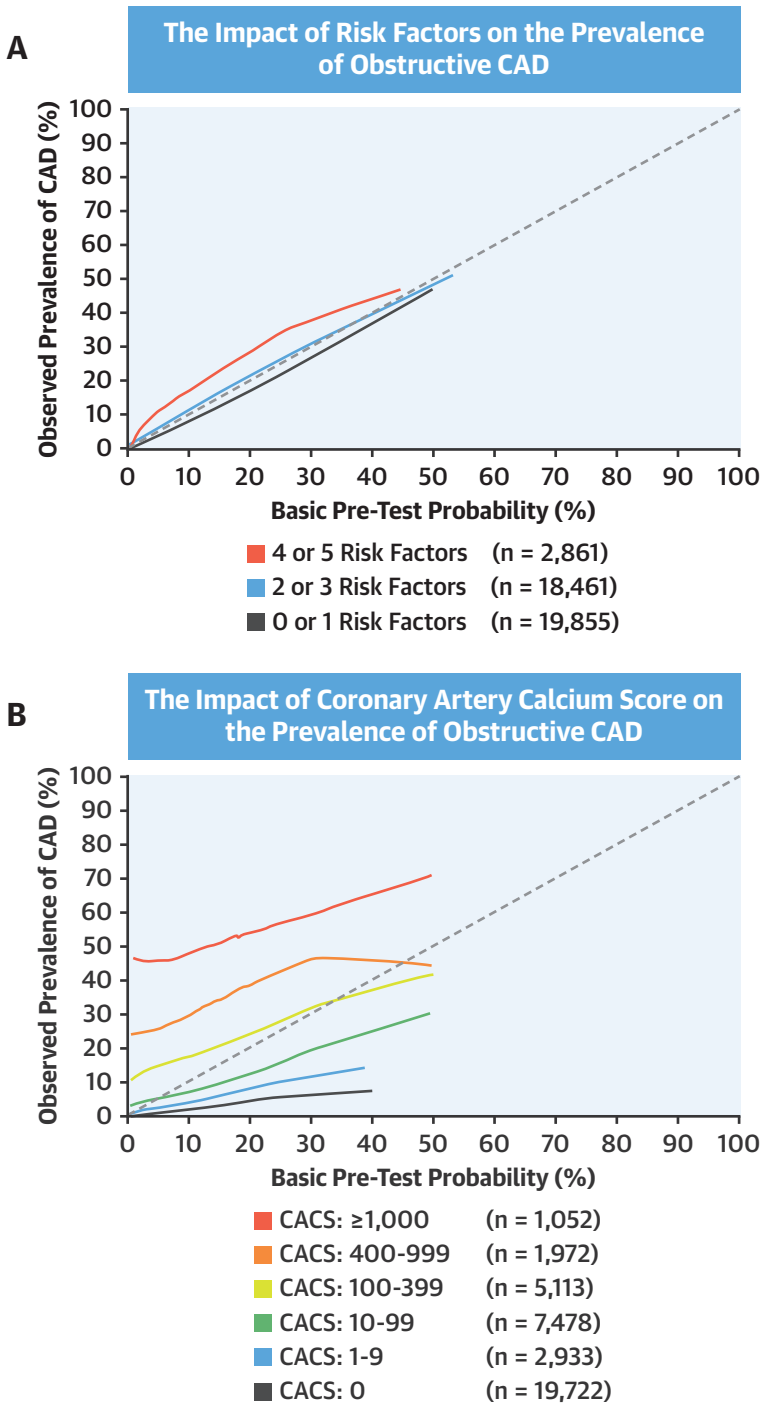
In total, 27.3% more patients in the validation cohort were below the cutoff value of 5% for predicted obstructive CAD when the RF-CL model was applied as compared with the PTP model, 5,919 (38.4%) patients versus 1,708 (11.1%) patients, respectively. The diagnostic performance variables are shown in **Figure 3** and Supplemental Figure 8. The positive and negative likelihood ratios were 1.51 (95% CI: 1.48 to 1.55) and 0.27 (95% CI: 0.24 to 0.31) for the 5% cut-off, respectively. The NRI tables showed substantial reclassification of patients to a lower likelihood category of CAD compared with the PTP model (Supplemental Table 5).

CACS-WEIGHTED PTP MODEL. The prevalence of obstructive CAD increased with increasing CACS in all basic PTP model patient categories (**Figure 1B**). Similarly, the prevalence of obstructive CAD also increased in all RF-CL categories with increasing CACS, and this was consistent across sex and age strata (Supplemental Figure 8).

As the impact of risk factors on the CACS model was limited (Supplemental Table 1B), we combined the risk factor-weighted model and CACS subgroups in a linear regression model when the CACS-weighted clinical likelihood (CACS-CL) model was developed (**Central Illustration**). The distribution of patients according to CACS-CL model is shown in **Figure 2B**. The calibration of the CACS-CL model was excellent in the validation cohorts (**Figure 3**, Supplemental Figures 6 and 7).

The diagnostic performance of the CACS-CL model (AUC: 87.5%; 95% CI: 86.6 to 88.3) was similar to the advanced machine learning model (AUC: 86.8%; 95% CI: 85.9 to 87.6) in the training cohort (Supplemental Table 1B). The AUC of the CACS-CL model in the validation cohort was 84.9 (95% CI:

FIGURE 1 The Impact of Risk Factors and CACS on the Prevalence of Obstructive CAD



(A) The number of risk factors has an impact on the observed prevalence of coronary artery disease (CAD) in all pre-test probability categories but the highest relative impact in the low pre-test categories. Risk factors included in the model are family history of early CAD, smoking, dyslipidemia, hypertension, and diabetes. **(B)** Coronary artery calcium score (CACS) has a major impact on the observed prevalence of CAD across all pre-test probability categories. The **dashed line** represents the ideal calibration for the basic pre-test probability model estimated from a fitted model based on age, sex, and type of symptoms. The graph is based on data from the training cohort (n = 41,177).

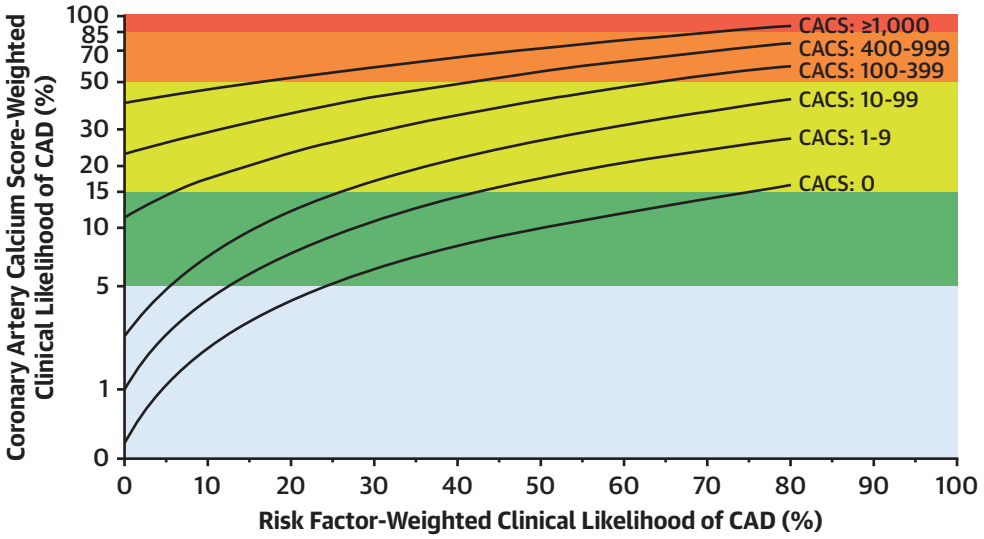
CENTRAL ILLUSTRATION **Estimation of the Clinical Likelihood of Obstructive Coronary Artery Disease**

A **Risk Factor-Weighted Clinical Likelihood**

	Nonanginal Pain						Atypical Angina or Dyspnea						Typical Angina					
	Women			Men			Women			Men			Women			Men		
Number of Risk Factors	0-1	2-3	4-5	0-1	2-3	4-5	0-1	2-3	4-5	0-1	2-3	4-5	0-1	2-3	4-5	0-1	2-3	4-5
Age: 30-39	0	1	2	1	2	5	0	1	3	2	4	8	2	5	10	9	14	22
Age: 40-49	1	1	3	2	4	8	1	2	5	3	6	12	4	7	12	14	20	27
Age: 50-59	1	2	5	4	7	12	2	3	7	6	11	17	6	10	15	21	27	33
Age: 60-69	2	4	7	8	12	17	3	6	11	12	17	25	10	14	19	32	35	39
Age: 70-80	4	7	11	15	19	24	6	10	16	22	27	34	16	19	23	44	44	45

Risk factors: *Family history, smoking, dyslipidemia, hypertension, diabetes*

B **Coronary Artery Calcium Score-Weighted Clinical Likelihood**



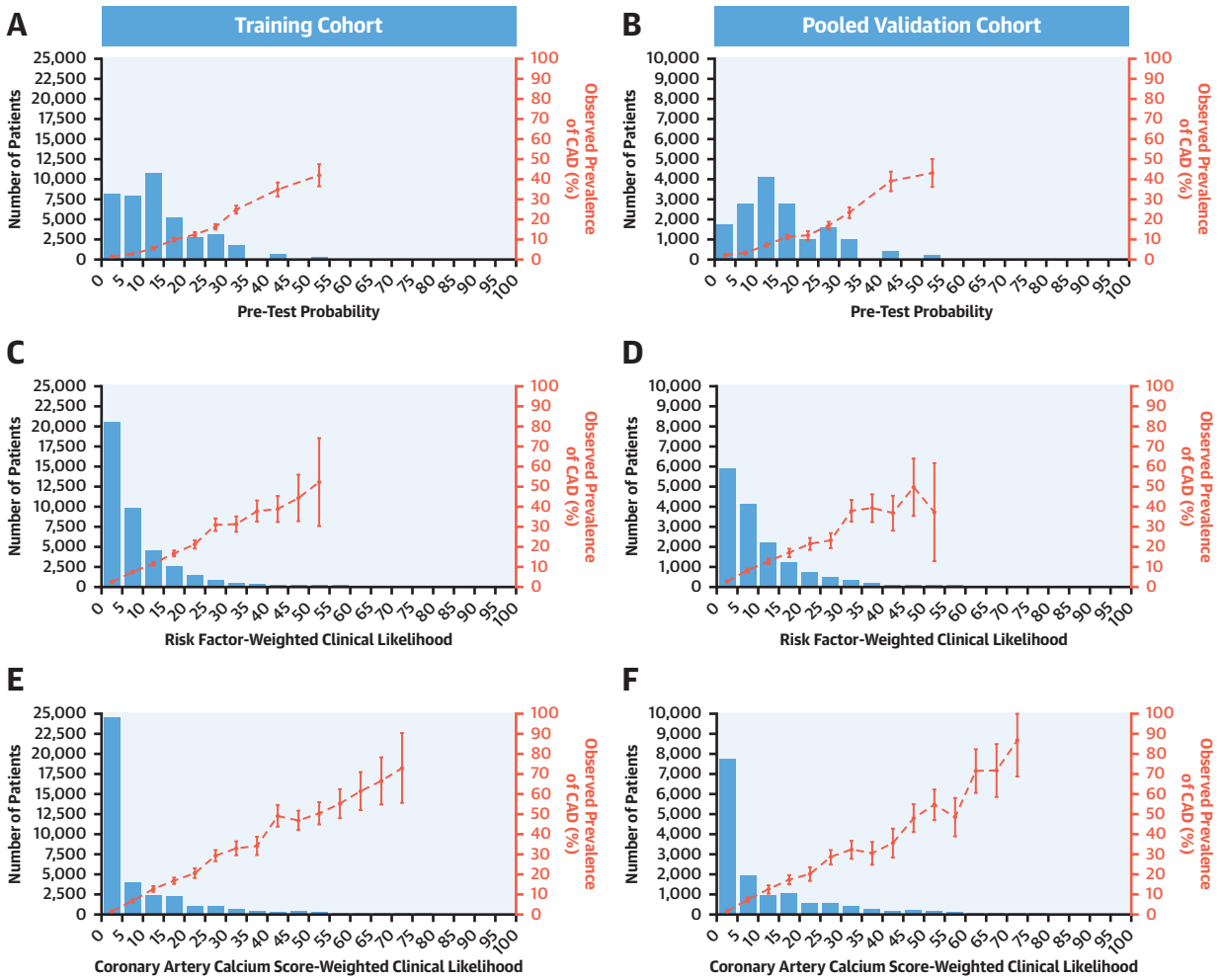
Winther, S. et al. J Am Coll Cardiol. 2020;76(21):2421–32.

Clinical likelihood of obstructive coronary artery disease (CAD) based on age, sex, type of symptoms, **(A)** number of risk factors and **(B)** coronary artery calcium score (CACS). 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 nitroglycerin 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. Dyspnea was defined as exertional dyspnea as the primary symptom.

84.0 to 85.9), which was higher than the AUCs of the PTP and the RF-CL models (Figure 3).

Substantially more patients (n = 7,801, 54.1%) in the validation cohort were below the cutoff value of 5% for predicted obstructive CAD when the CACS-CL model was applied compared with when the PTP and RF-CL models were applied. The diagnostic performance variables are shown in Figure 3, and sensitivity and specificity plots are shown in Supplemental Figure 9. The positive and negative likelihood ratios

FIGURE 2 Numbers of Patients and Observed Prevalence of CAD Across Categories of the 3 Models in the Training and Validation Cohorts



The number of patients **(bars)** and the prevalence of CAD with 95% confidence intervals **(red line)** for **(A, B)** the pre-test probability models and **(C, D)** the risk factor–weighted and **(E, F)** CACS-weighted clinical likelihood models in the training (n = 41,177) and the validation cohorts (n = 15,411). The figures show that the 2 new models reclassify more patients to low likelihood of CAD and that the observed prevalence of CAD remain very low in these categories. Importantly, the clinical likelihood model performance is stable in the validation cohort. Confidence intervals are shown only in groups with >10 patients. Abbreviations as in Figure 1.

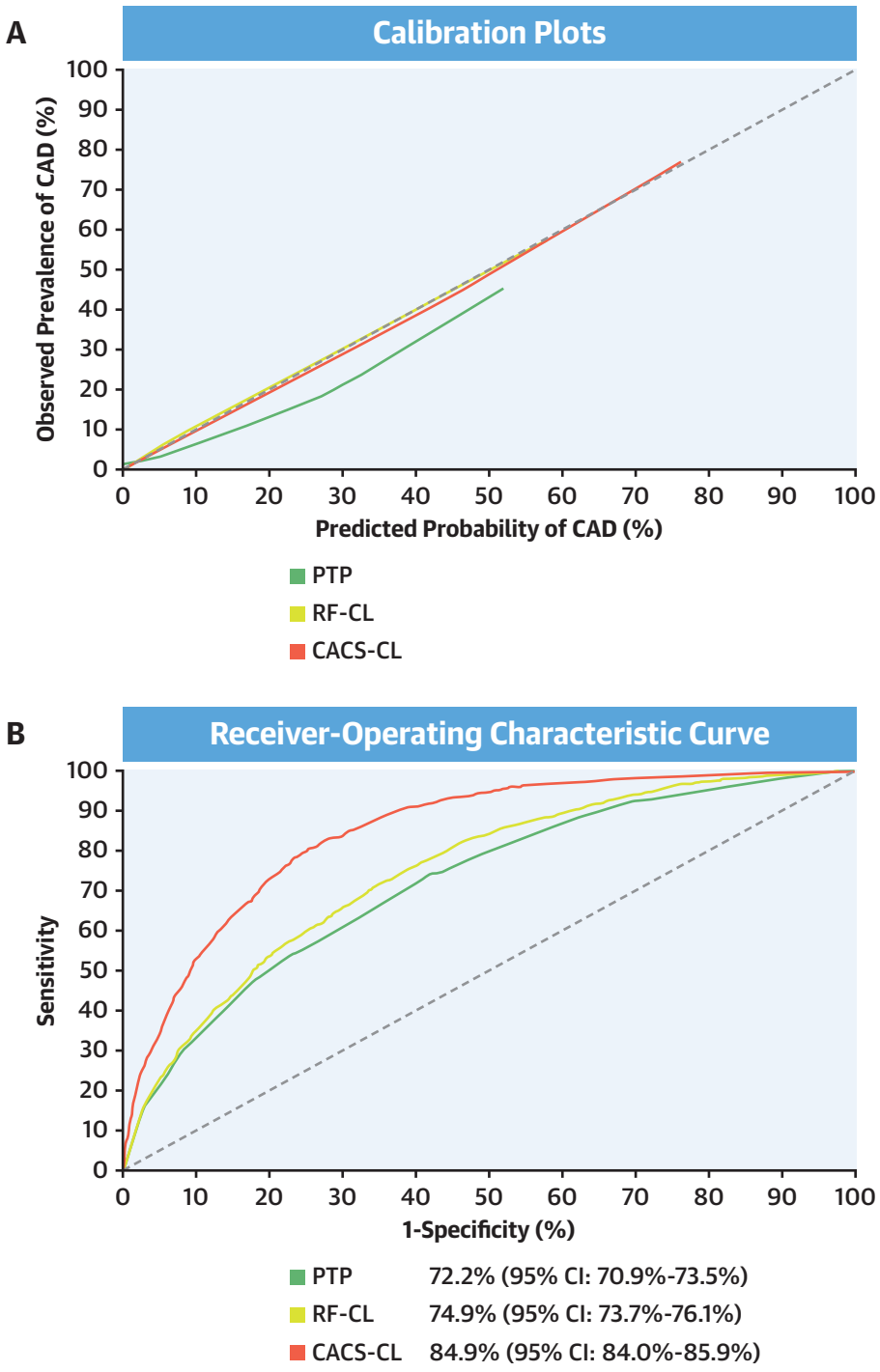
of the CACS-CL model with a 5% cut-off were 2.25 (95% CI: 2.19 to 2.31) and 0.14 (95% CI: 0.12 to 0.17), respectively. NRI tables showed substantial reclassification of patients to a lower likelihood category of CAD compared with the RF-CL model (Supplemental Table 6).

The performance of the RF-CL and CACS-CL models in comparison with the updated Diamond-Forrester score and the advanced CAD consortium models in the validation cohorts are presented in Supplemental Figures 6 and 7.

Sensitivity analysis showed that a modulated definition of the endpoint in the training cohort had a minor impact on the predicted disease probabilities in the models (Supplemental Figure 10). In addition, the final model discrimination was stable across a spectrum of endpoint definitions in the PROMISE trial (Supplemental Figure 11).

A stratified analysis for sex and age showed stable calibration and discrimination for the RF-CL model across sex and age strata (Supplemental Figure 12). However, the CACS-CL model calibration showed good performance in the groups between 50 and 70 years of age, but the model somewhat underestimated the observed prevalence among patients <50 of age years and overestimated the

FIGURE 3 Diagnostic Performance of the 3 Models



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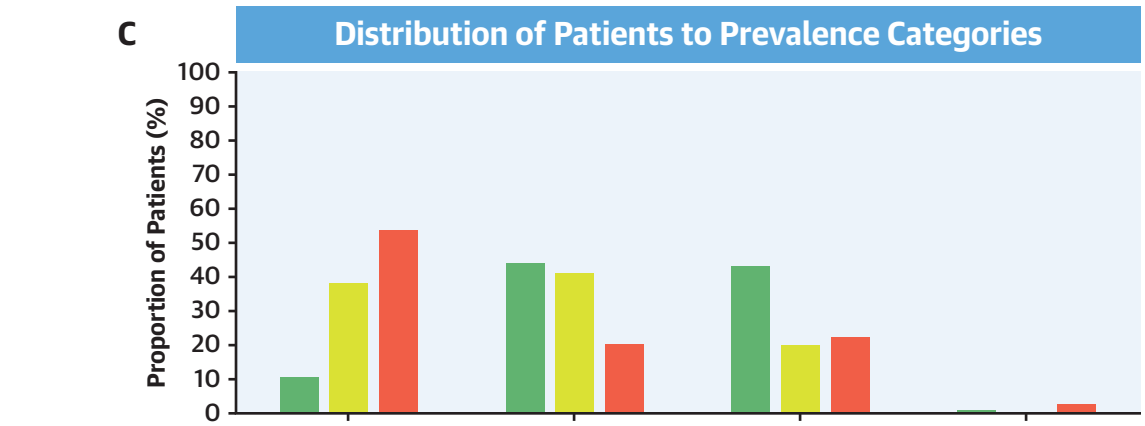
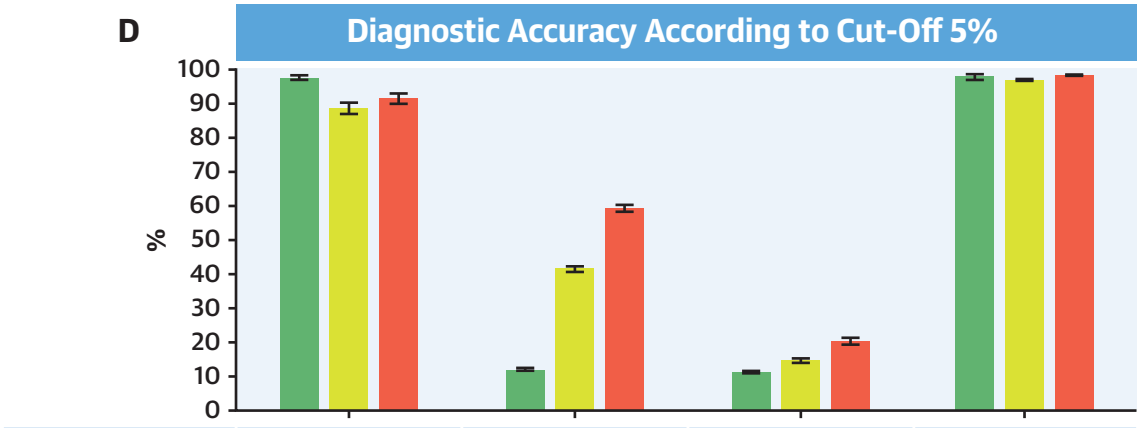
prevalence among patients with >70 years of age (Supplemental Figure 12). This difference is predominantly driven by patients with higher RF-CL and higher CACS values (Supplemental Figure 8). The CACS-CL calibration was stable among both male and female patients, and the CACS-CL discrimination was stable in all age and sex strata (Supplemental Figure 12). A secondary, stratified analysis of

FIGURE 3 Continued



Disease Prevalence	≤5%	>5%-≤15%	>15%-≤50%	>50%
PTP	2.2% (1.5%-2.9%)	5.5% (5.0%-6.1%)	16.0% (15.1%-16.9%)	43.0% (36.1%-49.9%)
RF-CL	3.0% (2.6%-3.4%)	10.0% (9.3%-10.7%)	24.0% (22.5%-25.5%)	35.3% (12.5%-58.0%)
CACS-CL	1.6% (1.3%-1.9%)	9.2% (8.1%-10.2%)	25.7% (24.3%-27.2%)	58.8% (54.0%-63.6%)



Diagnostic Accuracy	Sensitivity	Specificity	PPV	NPV
PTP	97.6% (96.8%-98.3%)	12.1% (11.5%-12.6%)	11.2% (10.7%-11.7%)	97.8% (97.0%-98.5%)
RF-CL	88.7% (87.0%-90.2%)	41.5% (40.7%-42.3%)	14.7% (14.0%-15.4%)	97.0% (96.5%-97.4%)
CACS-CL	91.5% (89.9%-92.8%)	59.3% (58.4%-60.1%)	20.4% (19.4%-21.4%)	98.4% (98.1%-98.7%)

Diagnostic performance parameters of obstructive CAD in the pooled validation cohorts (n = 15,411) for the 3 models, the pre-test probability model (PTP), the risk factor–weighted clinical likelihood (RF-CL) model and the CACS-weighted clinical likelihood (CACS-CL) model. **(A)** The calibration plots show good calibration of the new clinical likelihood models. **(B)** Receiver-operating characteristic curves show that discrimination increase in both the new clinical likelihood models but more substantially when CACS is included into the model. **(C)** The distribution of patients according to clinical likelihood cutoffs and the corresponding prevalence of obstructive CAD illustrate the reclassification ability of the models. **(D)** The diagnostic accuracy evaluated with sensitivity, specificity, and positive and negative predictive values with a clinical likelihood cutoff of 5% demonstrated that the negative predictive value remains very high despite a small drop in the overall sensitivity. CI = confidence interval.

ethnicity performed in the PROMISE trial showed stable calibration and discrimination of the RF-CL and CACS-CL models in non-Caucasian patients (n = 648), with AUCs of 71.1 (95% CI: 65.5 to 76.6) and 87.7 (95% CI: 84.3 to 91.1), respectively.

DISCUSSION

The current standard approach in patients with chronic coronary syndromes is to assess the PTP of obstructive CAD using sex, age, and type of

symptoms as proposed by Diamond and Forrester about 40 years ago (15). Over the last decades, the prevalence of CAD among patients undergoing diagnostic testing has decreased substantially, and the classic Diamond-Forrester model has been recalibrated several times (3,5,14,16,17). ESC guidelines recently suggested a novel concept of clinical likelihood of CAD as a more comprehensive and individualized assessment of the probability of disease. The guidelines, however, provide no specific tools for a clinical application (2). Advanced models that include risk factors have previously been suggested (14,18), and the present study fills this "gap in evidence" by validating a simple clinical tool for the individual estimation of clinical likelihood of CAD. We developed a simple RF-CL and CACS-CL tool, which enables a more accurate prediction and discrimination of patients with suspected obstructive CAD. Furthermore, the tool categorizes clearly more patients as having a low clinical likelihood of CAD as compared with standard model, and in these patients, further testing may be avoided.

The novelty and strength of the developed tool is that no calculations are needed, and all information can be extracted from a simple table and graph as shown in the **Central Illustration**. The tool was developed by stepwise simplification of advanced machine learning models without significant loss of accuracy.

Compared with patient characteristics and risk factors, CACS is known to be the strongest predictor of obstructive CAD (19). Accordingly, discrimination did not improve further in our study, when we included the specific risk factors into the CACS model as compared with the final CACS-CL model, which just combined the RF-CL and CACS. Of importance, CACS should not be used as a diagnostic test for obstructive CAD, as it does not measure noncalcified atherosclerosis plaque burden and stenosis severity. Hence, CACS represents only a surrogate for calcified coronary arteriosclerosis plaque burden. In the present study, we used CACS to further individualize the assessment of the likelihood of obstructive CAD. We found that CACS imaging had a major impact on the likelihood estimation of obstructive disease and particularly the CACS-CL models discrimination of obstructive CAD increased. Consequently, it may be considered as part of the early diagnostic work-up of patients with suspected CAD in the future. CACS also has the potential to guide preventive medical treatment, although CACS-driven randomized prevention trials are limited in patients with suspected CAD.

Interestingly, the discrimination of the models was lower in the Dan-NICAD and PROMISE trial cohorts than in the real-world registry cohorts. One explanation for this could be that the symptoms of the patients were less predictive of obstructive CAD in the Dan-NICAD and PROMISE trial cohorts than those in the registry patients (Supplemental Table 4), possibly due to different criteria for assessment of symptoms.

Using the RF-CL and CACS-CL models, 38% and 54% of the patients were classified with a very low (≤5%) clinical likelihood of CAD, respectively, and thus might not need routine diagnostic testing (2). Using the new models, the sensitivity dropped slightly, but the negative predictive value still remained very high (97.0% and 98.4%), which is important for the individual patient management (**Figure 3**). The CACS-CL model also reduced the number of patients in the "gray zone" of 5% to 15% clinical likelihood for CAD in whom diagnostic testing can be considered according to guideline recommendations.

Site reading of coronary CTA is known to overestimate the degree of stenosis. Therefore, we used an endpoint achieved by ICA on a clinical indication after the coronary CTA for establishment of the models in the training cohort. Theoretically, inclusion of the patients with suspected CAD on coronary CTA, who did not undergo ICA, can cause errors in the model. However, the sensitivity analysis showed that this issue had minor impact on the predicted disease probabilities (Supplemental Figure 10). In addition to temporal validation in the same cohort, we validated the models in the Dan-NICAD and PROMISE trials. In the Dan-NICAD trial, the reference standard was ICA with fractional flow reserve measurements. In the PROMISE trial, 23% of the patients had a ≥50% diameter stenosis by the site reading of coronary CTA, which were similar to the prevalence in WDHR 2008 to 2017, WDHR 2018 to 2019, and Dan-NICAD trial cohorts, 21%, 22%, and 22%, respectively. However, only 14% of the patients in the PROMISE trial had ≥50% diameter stenosis by the coronary CTA core lab reading and only 11% of the PROMISE trial cohort underwent ICA (Supplemental Table 4). Consequently, we used a combined endpoint defined as invasive quantitative coronary angiography stenosis or core lab CTA stenosis, when ICA was not performed. Sensitivity analysis of different endpoints in the PROMISE trial demonstrated stable discrimination (Supplemental Figure 11). In any case, the definition of CAD has a major impact on the prevalence of CAD and therefore also on the accuracy of the model calibration, and should therefore always be carefully considered.

STUDY LIMITATIONS. The patients included in the present study were referred for coronary CTA. Hence, some selection bias cannot be excluded. Patients with a very low likelihood of CAD are not consistently referred for diagnostic testing. In addition, patients with severe kidney disease or severe obesity may be under-represented, because all patients had to be eligible for coronary CTA. The validation was performed predominantly in Caucasian patients from European and North American. However, sensitivity analysis of the PROMISE trial data showed that race and ethnicity did not alter the diagnostic performance of the models.

CONCLUSIONS

A simple RF-CL and CACS-CL tool enabled improved prediction and discrimination of patients with chronic coronary syndromes. The models optimize reclassification of patients to low likelihood of CAD without need of further testing.

AUTHOR RELATIONSHIP WITH INDUSTRY

This work was supported by the Steno Partner Collaboration Unit, Gødstrup Hospital, Herning, Denmark. Drs. Winther, Schmidt, and Bøttcher have received institutional research grant support from Acarix. Dr. Schmidt is a part-time consultant for Acarix. Dr. Schmidt is a minor shareholder of Acarix. Dr. Hoffmann has received institutional research grants on behalf of Massachusetts General Hospital, outside of the submitted work, from KOWA, MedImmune, AstraZeneca, and HeartFlow; and has received consultant fees from DCRI and Recor, outside of the scope of the submitted work. Dr. Wijns has received research grants and honoraria from MicroPort. Dr. Christiansen has served on the Advisory Board for Novo Nordisk. Dr. Saraste has received speaker fees from AstraZeneca, Amgen, Bayer, Novartis, and Abbott; and has served on the Advisory Board for AstraZeneca and Amgen, outside of the submitted work. Dr. Bøttcher has served on the Advisory Board for Novo Nordisk, AstraZeneca, Bayer, Sanofi, and Acarix, outside of submitted work. Dr. Knuuti has received speaker fees from GE Healthcare, Merck, Lundbeck, and Bayer; and has received study protocol consultant fees from GE Healthcare and AstraZeneca, outside of the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In addition to a patient's age, sex, and symptoms, estimation of the PTP of CAD should consider family history of early CAD, smoking, dyslipidemia, hypertension, and diabetes. Incorporation of the CACS further improves accuracy.

TRANSLATIONAL OUTLOOK: Further studies are needed to evaluate the predictive value of this simple assessment method in well-defined subgroups of patients at risk of CAD.

REFERENCES

1. Hoorweg BB, Willemsen RT, Cleef LE, et al. Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses. Heart 2017;103:1727–32.

2. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407–77.

3. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: Executive Summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:2564–603.

4. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886–95.

5. Juarez-Orozco LE, Saraste A, Capodanno D, et al. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. Eur Heart J Cardiovasc Imaging 2019;20:1198–207.

6. Haase R, Schlattmann P, Gueret P, et al. Diagnosis of obstructive coronary artery disease using computed tomography angiography in patients with stable chest pain depending on clinical probability and in clinically important subgroups: meta-analysis of individual patient data. BMJ 2019;365:l1945.

7. Schmidt M, Maeng M, Madsen M, Sorensen HT, Jensen LO, Jakobsen CJ. The Western Denmark Heart Registry: its influence on cardiovascular patient care. J Am Coll Cardiol 2018;71:1259–72.

8. Nissen L, Winther S, Isaksen C, et al. Danish study of Non-Invasive testing in Coronary Artery Disease (Dan-NICAD): study protocol for a randomised controlled trial. Trials 2016;17:262.

9. Nissen L, Winther S, Westra J, et al. Diagnosing coronary artery disease after a positive coronary computed tomography angiography: the Dan-NICAD open label, parallel, head to head, randomized controlled diagnostic accuracy trial of cardiovascular magnetic resonance and myocardial perfusion scintigraphy. Eur Heart J Cardiovasc Imaging 2018;19:369–77.

10. Douglas PS, Hoffmann U, Lee KL, et al. PROspective Multicenter Imaging Study for Evaluation of chest pain: rationale and design of the PROMISE trial. Am Heart J 2014;167:796–803.e1.

11. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015;372:1291–300.

12. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J 2014;35:1925–31.

13. Pencina MJ, Goldstein BA, D'Agostino RB. Prediction models - development, evaluation, and clinical application. N Engl J Med 2020;382:1583–6.

14. Genders TS, Steyerberg EW, Hunink MG, et al. Prediction model to estimate presence of coronary

artery disease: retrospective pooled analysis of existing cohorts. BMJ 2012;344:e3485.

15. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 1979;300:1350–8.

16. Genders TS, Steyerberg EW, Alkadhi H, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J 2011;32:1316–30.

17. Foldyna B, Udelson JE, Karady J, et al. Pre-test probability for patients with suspected obstructive coronary artery disease: re-evaluating Diamond-Forrester for the contemporary era and clinical implications: insights from the PROMISE trial. Eur Heart J Cardiovasc Imaging 2019;20:574–81.

18. Pryor DB, Harrell FE Jr., Lee KL, Califf RM, Rosati RA. Estimating the likelihood of significant coronary artery disease. Am J Med 1983;75:771–80.

19. Winther S, Nissen L, Westra J, et al. Pre-test probability prediction in patients with a low to intermediate probability of coronary artery disease: a prospective study with a fractional flow reserve endpoint. Eur Heart J Cardiovasc Imaging 2019;20:1208–18.

KEY WORDS coronary artery calcium score, coronary artery disease, coronary stenosis, pre-test probability, risk factor

APPENDIX For an expanded Methods section as well as supplemental tables and figures, please see the online version of this paper.