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ORIGINAL RESEARCH

Performance of the American Heart Association/American College of Cardiology Guideline-Recommended Pretest Probability Model for the Diagnosis of Obstructive Coronary Artery Disease

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BACKGROUND: Substantial differences exist between different guideline-recommended pretest probability (PTP) models for the detection of obstructive coronary artery disease (CAD). This study was performed to study the performance of the 2021 American Heart Association/American College of Cardiology (AHA/ACC) guideline-recommended PTP (AHA/ACC-PTP) model in assessing the likelihood of obstructive CAD compared with previously proposed models.

METHODS AND RESULTS: Symptomatic patients (N=50 561) referred for coronary computed tomography angiography were included. The reference standard was invasive coronary angiography with optional fractional flow reserve measurements. The AHA/ACC-PTP values based on sex and age were calculated and compared with the 2019 European Society of Cardiology guideline PTP values based on sex, age, and symptoms as well as the risk factor–weighted clinical likelihood values based on sex, age, symptoms, and risk factors. The AHA/ACC-PTP maximum values overestimated by a factor of 2.6 the actual prevalence of CAD. Compared with the AHA/ACC-PTP model (area under the receiver-operating curve, 71.5 [95% CI, 70.7–72.2]), inclusion of typicality of symptoms in the European Society of Cardiology guideline PTP improved discrimination of CAD (area under the receiver-operating curve, 75.5 [95% CI, 74.7–76.3]). Inclusion of both symptoms and risk factors in the risk factor–weighted clinical likelihood model further improved discrimination (area under the receiver-operating curve, 77.7 [95% CI, 77.0–78.5]). The proportion of patients classified as very low PTP was lower using the AHA/ACC-PTP (5%) compared with the European Society of Cardiology guideline PTP (19%) and the risk factor–weighted clinical likelihood (49%) models.

CONCLUSIONS: The new AHA/ACC-PTP model overestimates the prevalence of obstructive CAD substantially if type of symptoms and risk factors are not taken into account. Inclusion of both symptoms and risk factors improves model performance and identifies more patients with very low likelihood of CAD in whom further testing can be deferred.

Key Words: chronic coronary syndrome ■ computed tomography angiography ■ coronary artery disease ■ coronary stenosis ■ pretest probability ■ stable coronary artery disease

See Editorial by Koifman and Giladi

Angina pectoris was first described by Dr William Heberden in 1772.[1] He described symptoms of angina pectoris as a strangling and/or painful sensation in the breast, located behind the sternum and more often inclined to the left than to the right side of the chest. Frequently the pain radiates from the breast to

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CLINICAL PERSPECTIVE

What Is New?

- Estimation of the pretest probability of obstructive coronary artery disease is recommended to guide patient management.
- Several models exist to estimate the clinical likelihood of disease, but there are substantial differences in the estimated probabilities between models, which impact patient management.

What Are the Clinical Implications?

- The 2021 American Heart Association/American College of Cardiology guideline-recommended pretest probability models provide only "maximal" values for patients with any chest pain; clinicians should downgrade this probability significantly.
- The risk factor–weighted clinical likelihood model has superior calibration, discrimination, and reclassification potential compared with both the 2019 European Society of Cardiology and 2021 American Heart Association/American College of Cardiology guideline-recommended pretest probability models.

Nonstandard Abbreviations and Acronyms

AHA/ACC	American Heart Association/American College of Cardiology
CTA	computed tomography angiography
ESC	European Society of Cardiology
ICA	invasive coronary angiography
PROMISE	Prospective Multicenter Imaging Study for Evaluation of Chest Pain
PTP	pretest probability
RF-CL	risk factor–weighted clinical likelihood
WDHR	Western Denmark Heart Registry

the left arm. Symptoms are related to walking, especially uphill, or soon after eating and vanish the moment the patient stands still.

Today, the typicality of angina is categorized according to the classic anginal symptoms as detailed above, including the classic location of discomfort, in addition to aggravating and relieving factors. Categorizing the chest pain experienced by the patient into typical angina, atypical angina, or nonanginal chest pain requires all 3 angina characteristics, only 2 of those characteristics, or 1 or none of these characteristics, respectively.[2,3]

Angina pectoris symptoms are common, with a life prevalence of 20% to 40%, resulting in millions of individuals undergoing evaluation for obstructive coronary artery disease (CAD) each year.[4] The diagnostic strategy in patients with symptoms suggestive of obstructive CAD starts with estimation of the pretest probability (PTP) to help guide the decision-making process on further diagnostic testing.[3,4] Traditionally, PTP tables based on sex, age, and type of symptoms have been used. The latest update of the PTP table, based on European and American patient cohorts, was published by Juarez-Orozco et al and adopted in the European Society of Cardiology (ESC) guidelines published in 2019 (ESC-PTP) (Figure 1).[3,5]

Recently, a more comprehensive assessment of CAD probability based on a simple table, including sex, age, and type of symptoms, combined with the number of cardiovascular risk factors was proposed and from which the risk factor–weighted clinical likelihood (RF-CL) model was derived (Figure 1).[6] In a large international validation cohort (n=15 411), the RF-CL enabled optimized reclassification of patients and improved prediction and discrimination of obstructive CAD compared with the ESC-PTP model.[6]

In the new 2021 American Heart Association/American College of Cardiology (AHA/ACC)/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain (AHA/ACC-PTP) (Figure 1), categorization of the symptom typicality was not included in the PTP estimation.[7] The justification for this exclusion was that not only chest pain should be considered angina equivalents, but also pressure, tightness, or discomfort in the chest, shoulders, arms, neck, back, upper abdomen, or jaw, as well as shortness of breath and fatigue. Furthermore, this exclusion was meant to reduce the confusion on the terminology of atypical angina. Correspondingly, the 2021 guideline provides only sex- and age-stratified "maximal" PTP estimations for patients with chest pain but does not provide any supportive data for the PTP estimations based on nonclassic symptoms as well as presence or absence of risk factors. The guideline includes a visual graph to downgrade PTP based on symptoms, but no specific guidance or data are provided.

The aim of this study was to investigate whether categorization of angina typicality and risk factor assessment improve stratification of patients according to their observed prevalence of disease in a contemporary cohort of patients with suspected obstructive CAD. Second, we studied the clinical consequences of applying the simplified AHA/ACC-PTP model compared with the ESC-PTP and the RF-CL models.

METHODS

Study Population

This cohort study was performed using the WDHR (Western Denmark Heart Registry), a Danish population-based quality assurance database.[8] We identified all patients who received first-time coronary

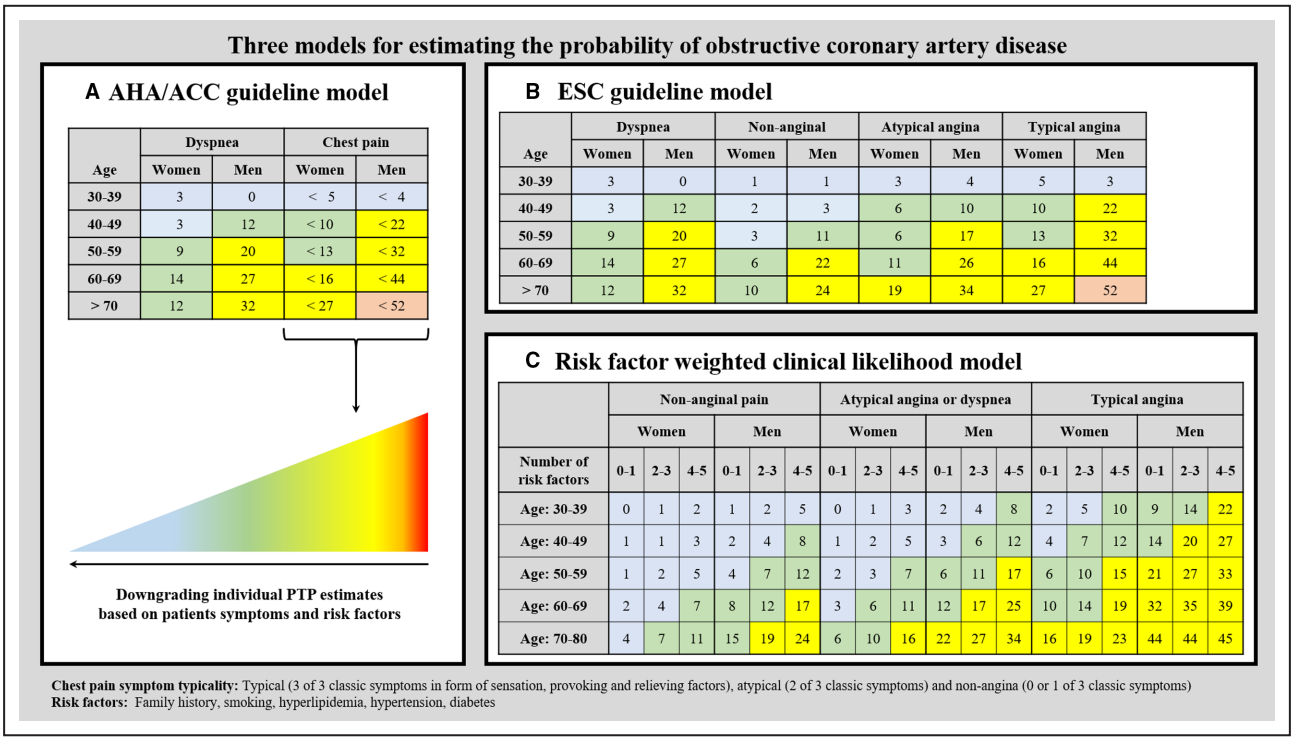


Figure 1. The predicted pretest probability (PTP) table from the 2021 American Heart Association/American College of Cardiology (AHA/ACC) Guideline for the Evaluation and Diagnosis of Chest Pain (A), 2019 European Society of Cardiology (ESC) guidelines for the diagnosis and management of chronic coronary syndromes (B), and the risk factor–weighted clinical likelihood model (C).

computed tomography angiography (CTA) from 2008 to 2019 at 13 hospitals that cover Western Denmark, with a population of around 3.3 million (55% of the total Danish population). The cohort of interest included all adult patients without previously known CAD. Coronary CTA is the nationally preferred and recommended first-line test for suspected CAD.[9]

Eligible patients were typically referred to cardiology outpatient clinics by general practitioners after presenting with symptoms of stable CAD. All patients with symptoms suspect of CAD underwent a clinical assessment, including echocardiography, and were referred for coronary CTA. In patients who had received >1 coronary CTA, only the first scan was used in the current analysis. Patients who had incomplete information on the coronary CTA or chest pain symptoms were excluded.

The WDHR contains information on all coronary CTAs and invasive coronary angiography (ICA) scans performed in the western part of Denmark. It is mandatory for the treating cardiologist to report baseline characteristics as well as coronary CTA and ICA results to this database. The information is based on the clinical evaluation and includes data on cardiac risk factors and symptoms at the time of referral for coronary CTA. The study was approved by the Danish Data Protection Agency (record number 1-16-02-388-19). Informed consent was not required. Data can only be shared on request to the corresponding author and after a new approval from the Danish Data Protection Agency.

PTP Model Derivation

Age, sex, and symptom characteristics were used to calculate the AHA/ACA-PTP and ESC-PTP according to the tables in the respective guidelines.[3,7] The RF-CL table model included age, sex, symptom characteristics, and the number of risk factors (family history, smoking, hyperlipidemia, hypertension, and diabetes) categorized into 0 to 1, 2 to 3, and 4 to 5 risk factors.[6]

Coronary CTA

Both a non–contrast- and a contrast-enhanced examination were conducted using a variety of scanners (minimum, 64 detector row scanners). National recommendations for optimal image acquisition of coronary CTA advise, if necessary, use of β-blockers to target a heart rate of <60 beats per minute, and nitroglycerine administration. The coronary CTAs were analyzed locally and reported to the WDHR. No CAD was defined in the absence of coronary artery calcium and no coronary stenosis. A coronary CTA with a ≥50% diameter reduction in any coronary segment was identified as suspected stenosis.

Invasive Coronary Angiography

A postcoronary CTA 120-day window was used to categorize patients as to whether an ICA or revascularization had been performed in connection with the CTA. ICA was performed according to standard clinical practice, with fractional flow reserve measurements performed at the discretion of the investigating cardiologist. The ICA was interpreted locally and reported to the WDHR. Obstructive CAD was defined as a ≥50% diameter reduction in any coronary segment or fractional flow reserve ≤0.80 at ICA when performed within 120 days of the coronary CTA. Nonobstructive disease was defined as no obstructive CAD at ICA or when based on the CTA results that no ICA was needed.

Statistical Analysis

Continuous variables are presented as mean (±SD), and categorical variables are presented as number (percentage). Calibration and discrimination of the ACA/AHA-PTP, ESC-PTP, and RF-CL scores were evaluated according to current recommendations.[10] First, a calibration plot of the mean predicted probability and the mean observed proportion of minimal risk with flexible calibration (Loess bandwidth, 0.8) were evaluated. In addition, calibration in the large and calibration slope were presented, and the mean overestimation of the AHA/ACC was calculated from the calibration slope. The discrimination C-statistic included the area under the receiver-operating curve and net reclassification index. Statistical analysis was performed using STATA-17 (StataCorp, College Station, TX).

RESULTS

We included 50 561 patients without previously documented CAD, but with symptoms suggestive of obstructive CAD (Figure S1). Baseline demographics of the included patients as well as the coronary CTA and ICA results are presented in the Table. In summary, 54% of patients were women, and the mean age was 57±12 years. The distribution of patient symptom typicality was as follows: 12% typical angina, 48% atypical angina, 31% nonanginal chest pain, and 8% without chest discomfort but dyspnea as the predominant symptom. In total, 4034 (8.0%) patients were diagnosed with obstructive CAD at ICA.

Impact of Symptoms and Risk Factors on Obstructive CAD

The relationship between the observed prevalence of obstructive CAD and age, when stratified for symptom typicality, is presented in Figure 2. The prevalence of observed obstructive CAD was substantially higher among men, older patients, and patients with typical

Table. Patient Demographics

Variable	Value
No. (%) of patients	50 561 (100)
Characteristics	
Sex, male	23 395 (46.3)
Age, y	57.3±11.5
<40	3434 (6.8)
40 to<50	9620 (19.0)
50 to<60	15 717 (31.1)
60 to<70	14 757 (29.2)
≥70	7033 (13.9)
Family history of CAD	20 086 (39.7)
Smoking	
Never	19 680 (38.9)
Former	16 294 (32.2)
Active	10 304 (20.4)
Missing	4283 (7.1)
Hypercholesterolemia	14 855 (29.4)
Hypertension	18 006 (35.6)
Diabetes	3549 (7.0)
Symptoms	
Typical angina	6221 (12.3)
Atypical angina	24 393 (48.2)
Nonanginal chest pain	15 890 (31.4)
Dyspnea	4057 (8.0)
Pretest probability models, %	
AHA/ACC-PTP model	16 (13–32)
ESC-PTP model	11 (6–19)
RF-CL model	5 (2–11)
Coronary computed tomography angiography	
Coronary artery calcium score*	0 (0–76)
Disease severity by coronary CTA	
No CAD (no coronary calcium or stenosis)	20 923 (41.4)
Nonobstructive CAD (diameter stenosis <50%)	12 769 (37.6)
Coronary stenosis (diameter stenosis ≥50%)	10 628 (21.0)
Invasive coronary angiography and revascularization within 120 d of the coronary CTA	
Invasive coronary angiography	8566 (16.9)
Disease severity by ICA	
Obstructive coronary stenosis (diameter stenosis ≥50% and/or invasive fractional flow reserve <0.8)	4034 (8.0)
Revascularization	
Percutaneous coronary intervention	2451 (4.9)
Coronary artery bypass grafting	692 (1.4)

Baseline characteristics of included patients and the coronary CTA and ICA results. Values are number (percentage), mean±SD, or median (interquartile range). AHA/ACC indicates American Heart Association/American College of Cardiology; CAD, coronary artery disease; CTA, computed tomography angiography; ESC, European Society of Cardiology; ICA, invasive coronary angiography; PTP, pretest probability; and RF-CL, risk factor–weighted clinical likelihood.

*Coronary artery calcium score was missing in 6.8% of the patients.

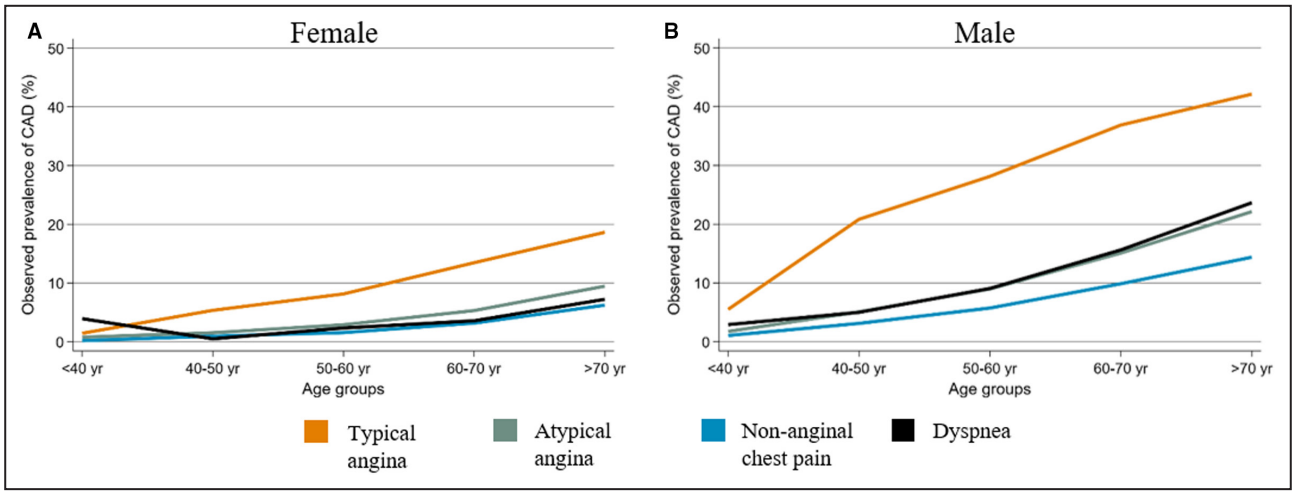


Figure 2. Observed prevalence of obstructive coronary artery disease (CAD), according to age (year) and sex.
A, Female patients. **B**, Male patients.

angina. There was an association between higher prevalence of obstructive CAD and number of risk factors in all age, sex, and symptom typicality subgroups (Figure 3).

Calibration of the PTP Models

In contrast to the observed prevalence of obstructive CAD of 8.0%, the median predicted prevalence of the AHA/ACC-PTP was 16% ((95% CI), 13%–32%). In the ESC-PTP, this was 11% (95% CI, 6%–19%), whereas for RF-CL, this was 5% (95% CI, 2%–11%). The mean observed prevalence of obstructive CAD for each AHA/ACC category is presented in Figure S2.

The AHA/ACC-PTP model overestimated the observed prevalence of CAD, whereas the ESC-PTP mildly overestimated the prevalence, and the RF-CL had a good calibration (Figure 4A). These findings were supported by statistical analysis of the calibration in the large and calibration slope from the calibration plots (Figure S3). Furthermore, the calibration slope showed an overestimation of the probability of disease with the AHA/ACC model by a factor of 2.6 (95% CI, 2.6–2.7); a more pronounced overestimation was present for patients with chest pain (2.7 [95% CI, 2.6–2.8]) compared with patients with dyspnea (1.8 [95% CI, 1.7–2.0]). The overestimation was most pronounced in patients with nonanginal chest pain (4.8 [95% CI, 4.5–5.1]) and atypical angina (3.1 [95% CI, 2.9–3.2]) compared with typical angina (1.2 [95% CI, 1.2–1.3]), which is summarized in Figure 5.

Discrimination of Obstructive CAD

When comparing the ability of the 3 models to discriminate between patients with versus without obstructive CAD, the AHA/ACC-PTP model had lower accuracy compared with the ESC-PTP (P<0.001), and the RF-CL had the highest accuracy (P<0.001); area under the receiver-operating curve values were 71.5 (95% CI, 70.7–72.2), 75.5 (95% CI, 74.7–76.3), and 77.7 (95% CI, 77.0–78.5), respectively (Figure 4B).

Reclassification With PTP Models

Distributions of patients according to PTP value groups and the observed prevalence of obstructive CAD in each group are presented for the 3 models in Figure 6 and Figure S4.

Using the AHA/ACC-PTP, 2282 (4.5%) patients were categorized to very low probability (PTP ≤5%) and 17 782 (35.2%) patients into very low or low probability (PTP ≤15%). In contrast, with the ESC-PTP, 9618 (19.0%) were categorized to very low probability and 32 327 (63.9%) into very low or low probability. Finally, with the RF-CL models, 24 590 (48.6%) patients were categorized to very low probability and 42 599 (84.3%) patients into very low or low probability.

Reclassification tables and net reclassification index are presented in Figure S5.

DISCUSSION

In the present study, the assessment of probability of obstructive CAD according to the 2021 AHA/ACC guideline on chest pain was evaluated.[7] Increasing evidence supports a pretest probability-guided use of diagnostic testing. The benefits include more effective use of the diagnostic tests and avoidance of unnecessary testing. However, the benefits can be achieved only when the applied PTP values are correctly reflecting the prevalence of CAD in the population.

The new simplified model in the AHA/ACC guideline provides only estimates for the “maximal” PTP values of obstructive CAD in patients with chest pain.[7]

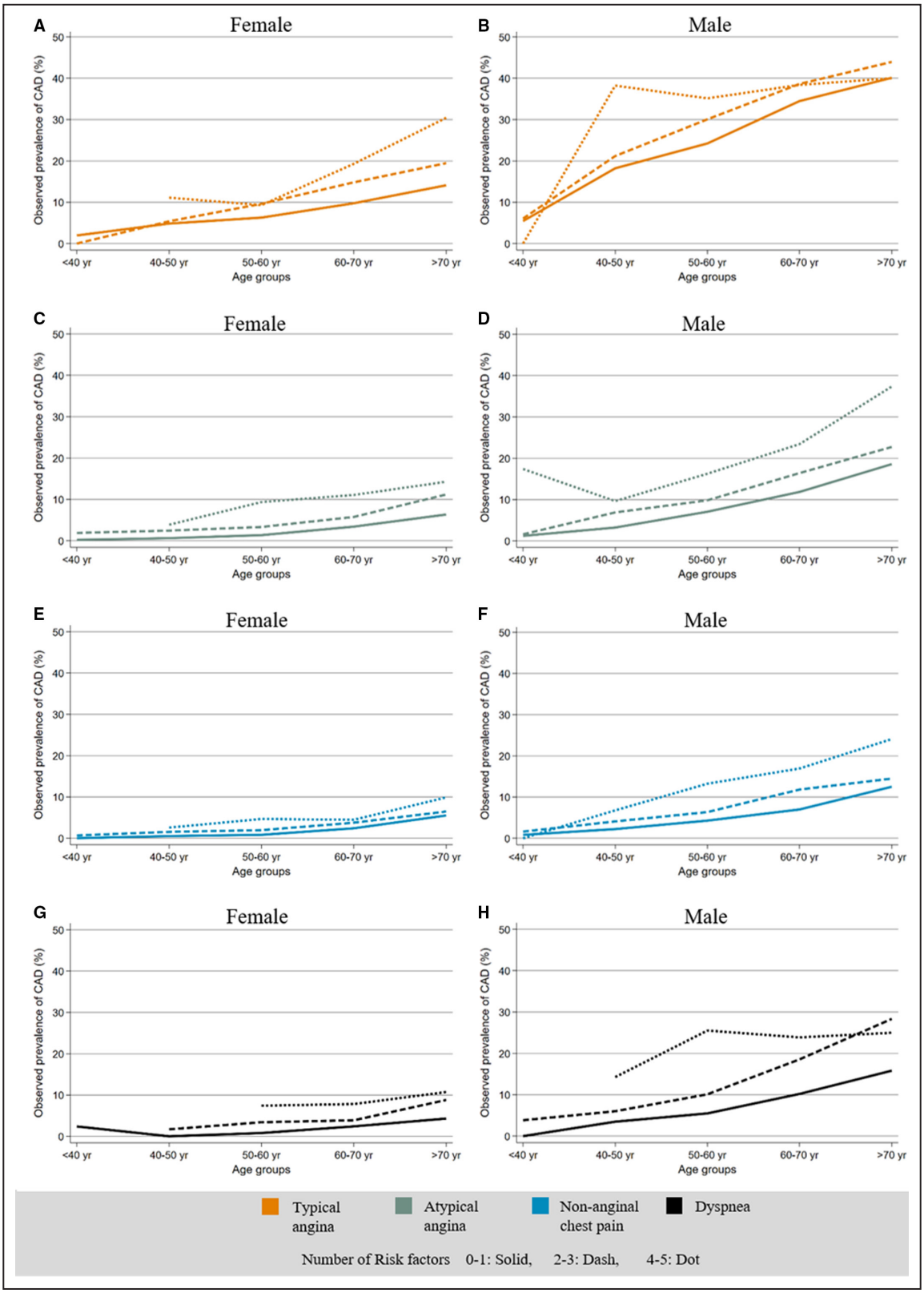


Figure 3. Correlation between observed prevalence of obstructive coronary artery disease (CAD) at invasive coronary angiography and age (year) when stratified for numbers of risk factors in sex and symptom subgroups (panel A–H).

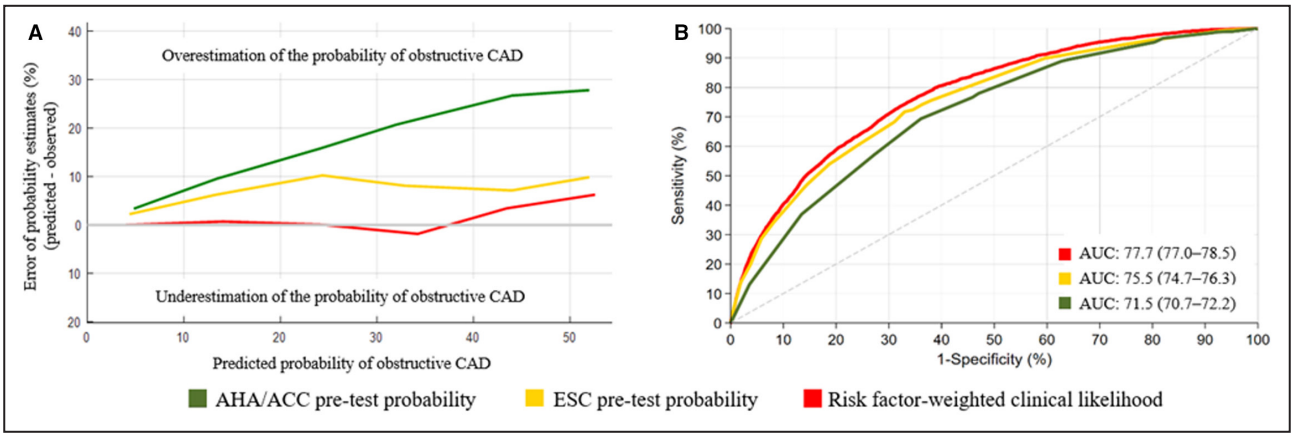


Figure 4. Calibration plots showing the error in predicting obstructive coronary artery disease (CAD) by the 3 models (A) and the receiver-operator curves for the 3 pretest probability models compared with a reference (B).
AHA/ACC indicates American Heart Association/American College of Cardiology; AUC, area under the receiver-operating curve; and ESC, European Society of Cardiology.

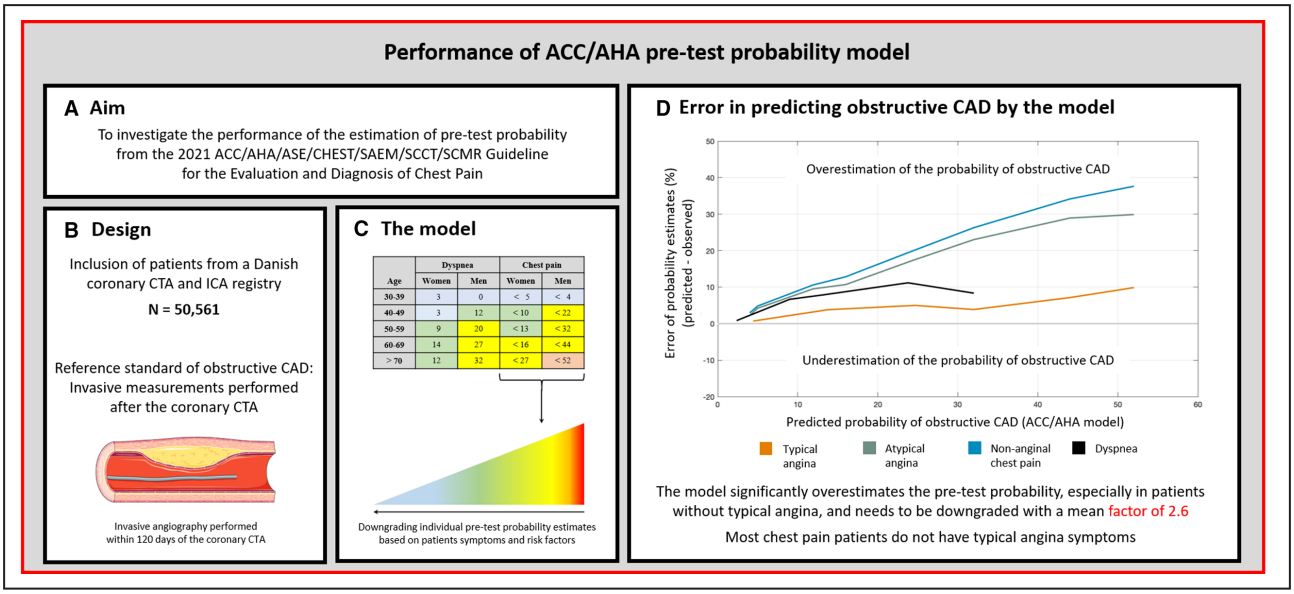
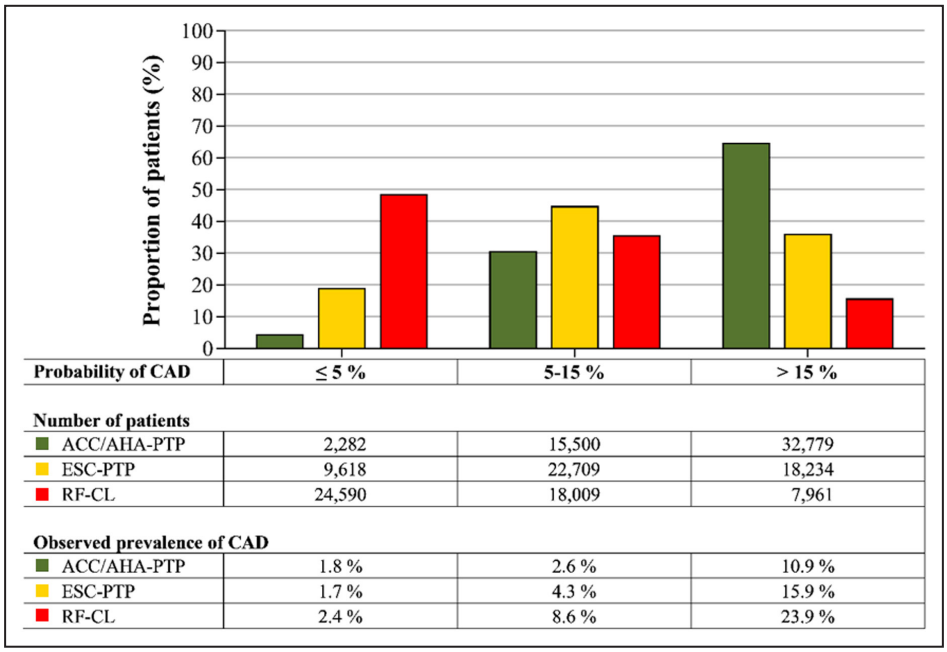


Figure 5. The 2021 American College of Cardiology/American Heart Association (ACC/AHA) guideline-recommended estimation of pretest probability with a model without stratification, according to chest pain symptom typicality.
Present study aim and design is summerized (**A**–**C**) and the study results demonstrated the need for substantial downgrading of the pretest probability estimates by clinicians based on patient symptoms and risk factors (D). CAD indicates coronary artery disease; CTA, computed tomography angiography; and ICA, invasive coronary angiography.

The guideline recommends that the clinicians should downgrade the PTP estimates using information about the type of symptoms and risk factors but provides no concrete tools apart from a graph with visual down ramping of PTP in patients with less typical symptoms. On the basis of the current analysis, the PTP values in the guideline are overestimated on average by a factor of 2.6 in patients with any chest pain. In patients with nonanginal chest pain and atypical angina, the overestimation was a factor of 4.8 and 3.1, respectively. The current analysis also demonstrates that with inclusion of the type of symptoms and risk factors, as performed in the RF-CL model, accurate classification is feasible and leads to substantial PTP down-classification, resulting in 47% of patients having a likelihood of obstructive CAD ≤5%.

In general, high-quality clinical prediction models should enable simple and accurate estimation of individual probabilities of disease to guide patient management. Hence, an accurate model will discriminate between disease and no disease and hold good calibration, meaning that predicted values equal the observed prevalence of disease. Finally, a good model will reclassify patients up or down and



Probability of CAD	≤ 5 %	5-15 %	> 15 %
Number of patients			
ACC/AHA-PTP	2,282	15,500	32,779
ESC-PTP	9,618	22,709	18,234
RF-CL	24,590	18,009	7,961
Observed prevalence of CAD			
ACC/AHA-PTP	1.8 %	2.6 %	10.9 %
ESC-PTP	1.7 %	4.3 %	15.9 %
RF-CL	2.4 %	8.6 %	23.9 %

Figure 6. Distributions of patients according to pretest probability (PTP) value groups and the observed prevalence of obstructive coronary artery disease (CAD) in each group for the 3 models.
ACC/AHA indicates American College of Cardiology/American Heart Association; ESC, European Society of Cardiology; and RF-CL, risk factor–weighted clinical likelihood.

thereby reduce the number of patients in the gray-zone area where management is uncertain. After development of such an accurate model, relevant cutoff for patient management should be proposed and validated.

The 2019 ESC guideline proposed updated PTP values of the standard Diamond-Forrester approach (PTP table based on age, sex, and type of symptoms) introduced in 1979.[2] Mean values from 3 large studies were used to create pooled PTP estimates by Juarez-Orozco et al.[5] The ESC-PTP model showed good calibration and ability to recalibrate patients compared with previous models.[11] The ESC guideline introduced the concept of clinical likelihood to highlight the fact that other factors than age, sex, and type of symptoms may decrease or increase the PTP values (eg, risk factors and coronary artery calcium score), and that these modifying factors should be taken into account in the individual evaluation.[12]

The AHA/ACC-PTP used the same pooled analysis as the ESC-PTP to generate the values presented.[5] Moreover, in patients with dyspnea, the AHA/ACC guideline presented similar mean PTP values. However, in contrast to the ESC guideline, the AHA/ACC guideline did not stratify patients with chest pain according to symptom typicality but presented "maximal" mean values for patients with any chest pain. For example, a 62-year-old man with any chest pain will have a PTP of <44%. However, this "maximal" value has been derived from data that are based on symptom typicality, an approach that the new AHA/ACC guidelines did not include. Therefore, on average, the PTP is overestimated in patients without typical angina. On the other hand, the PTP values may also be underestimated because the risk factors are not taken into account. For example, a 38-year-old male patient with typical angina and 4 to 5 risk factors will have a likelihood of obstructive CAD of 22% with the RF-CL model compared with <4% in the new 2021 AHA/ACC-PTP. These examples emphasize the importance of modifying the individual PTP by taking into account the characteristics of symptoms and risk factors. Of note, we do not know which guideline has the best outcome prediction because this has not been tested.

To date, it is unknown what is the optimal PTP cutoff value to defer testing, because no studies have investigated this according to symptom relief, quality of life, or prognosis. The cutoff recommended for deferring testing is 5% in the ESC guidelines, and testing with PTP of 5% to 15% could be considered on the basis of individual assessment. In the AHA/ACC guideline, testing was recommended in patients with PTP >15% and can be considered with PTP ≤15% based on clinical judgment.[3,7] Interestingly, the mean observed prevalence of disease was 14.9% in the data from which the PTP was estimated.

Using the AHA/ACC-PTP, only 5% of patients would be allocated to the very low probability category (PTP ≤5%), 31% of patients are in the gray zone (PTP 5%–15%), and 65% are categorized as PTP >15% based on the maximum values in the table before downgrading. In contrast, using the RF-CL model, 49% of patients would be categorized to a likelihood ≤5%, 35% of patients are in the gray zone between 5-15% and only 16% of patients to a likelihood >15%. Hence, the RF-CL model categorized clearly fewer patients to the intermediate-high PTP in which testing is recommended and more patients into the very low PTP in which testing is not recommended. As the goal of the AHA/ACC guideline was to avoid unnecessary testing, the findings of the present analysis emphasize that clinicians should downgrade the AHA/ACC-PTP maximum values.

In addition to the RF-CL model, we have also suggested a PTP model that includes the coronary artery calcium score.[6] The simple coronary artery calcium score clinical likelihood graphical tool has showed superiority to both ESC-PTP and use of coronary calcium alone, therefore further improving the classification and increasing the number of patients with very low PTP.[6,13] Part of these data was also adopted into the 2021 AHA/ACC guidelines on chest pain.[7] However, in which patients coronary artery calcium score testing is most beneficial for clinical decision-making is still unknown. In addition, whether inclusion of factors, such as genetic risk variants, circulating biomarkers, or other simple tests, can increase performance of clinical likelihood models needs further investigation.

LIMITATIONS

The validation was performed in the WDHR, which represents predominantly White patients. Other races and ethnic groups may experience or describe their symptoms differently, and further validation is needed. Inherent to the observational design of the present study, there is a risk of referral and selection bias. Patients were referred for coronary CTA, which may have introduced some bias as patients with very low likelihood are not referred for testing. Furthermore, patients with severe kidney disease and arrhythmias or severe obesity are not investigated with coronary CTA and therefore the reference population may not reflect the full spectrum of disease.

The RF-CL model was previously developed from the WDHR over the years 2008 to 2017 (n=41 178). However, temporal validation in the years 2018 to 2019 (n=9383) showed consistent good calibration (Figure S6). Furthermore, the RF-CL model showed consistently high performance when externally validated in 4403 American patients included in the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) and 4207 patients included at the Tianjin Chest Hospital, China.[6,13,14]

In the current cohort, we used ICA as the reference standard for obstructive CAD, including fractional flow reserve, when performed on the basis of a clinical indication. With this end point, we observed a CAD prevalence of only 8%, which is low compared with other cohorts. In contrast, the prevalence of CAD in the pooled cohort from which the guideline-recommended models were developed was 14.9%. However, the probabilities of CAD in these 3 studies were highly impacted by the definition of CAD. Reeh et al (n=3294) used ICA and had a disease prevalence of 7.4%, the PROMISE study (n=4415) used core-laboratory reading of coronary CTA and had a disease prevalence of 13.9%, and the International Coronary CT Angiography Evaluation for Clinical Outcomes Registry (n=8106) study used site reading of coronary CTA and had a disease prevalence of 18.4%.[15–17]

CONCLUSIONS

On the basis of testing in a large contemporary cohort, the 2021 AHA/ACC guideline on chest pain recommended PTP models based on age and sex overestimate the probability of CAD when using the given "maximal" values. Clinicians should therefore substantially reduce these values during patient consultation to ensure accurate estimation of the probability of obstructive CAD.

Use of more granular symptom classification, inclusion of risk factors, yields more accurate estimation of PTP with an increased reclassification potential and more patients in whom further testing can be deferred. Because of the superiority of the RF-CL model and previous external validation, we would recommend clinicians to use this model for accurate individualized calculation of patients' PTP of obstructive CAD.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Figure S1–S6

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SUPPLEMENTAL MATERIAL

Figure S1. Study design.

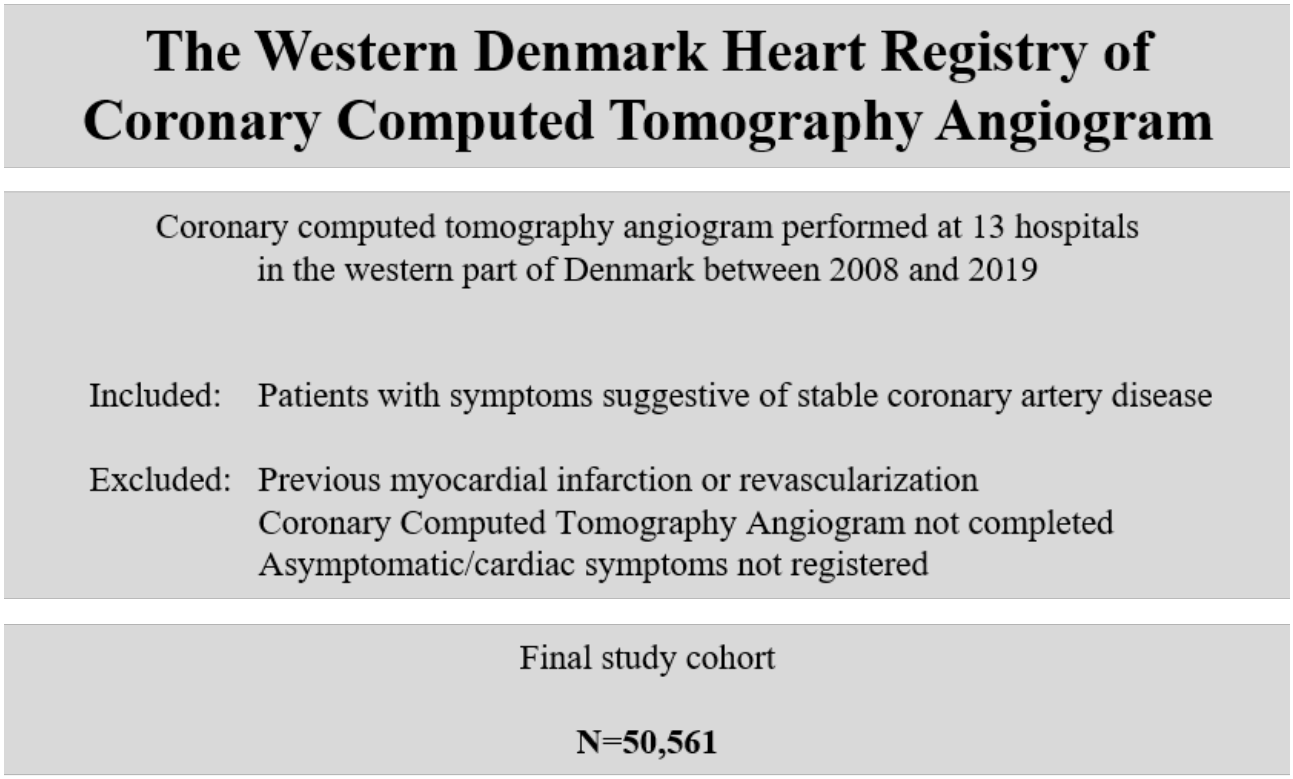


Figure S2. Tables of the observed prevalence of obstructive coronary artery disease compared to the AHA/ACC guideline PTP estimates.

A) Observed prevalence of obstructive CAD

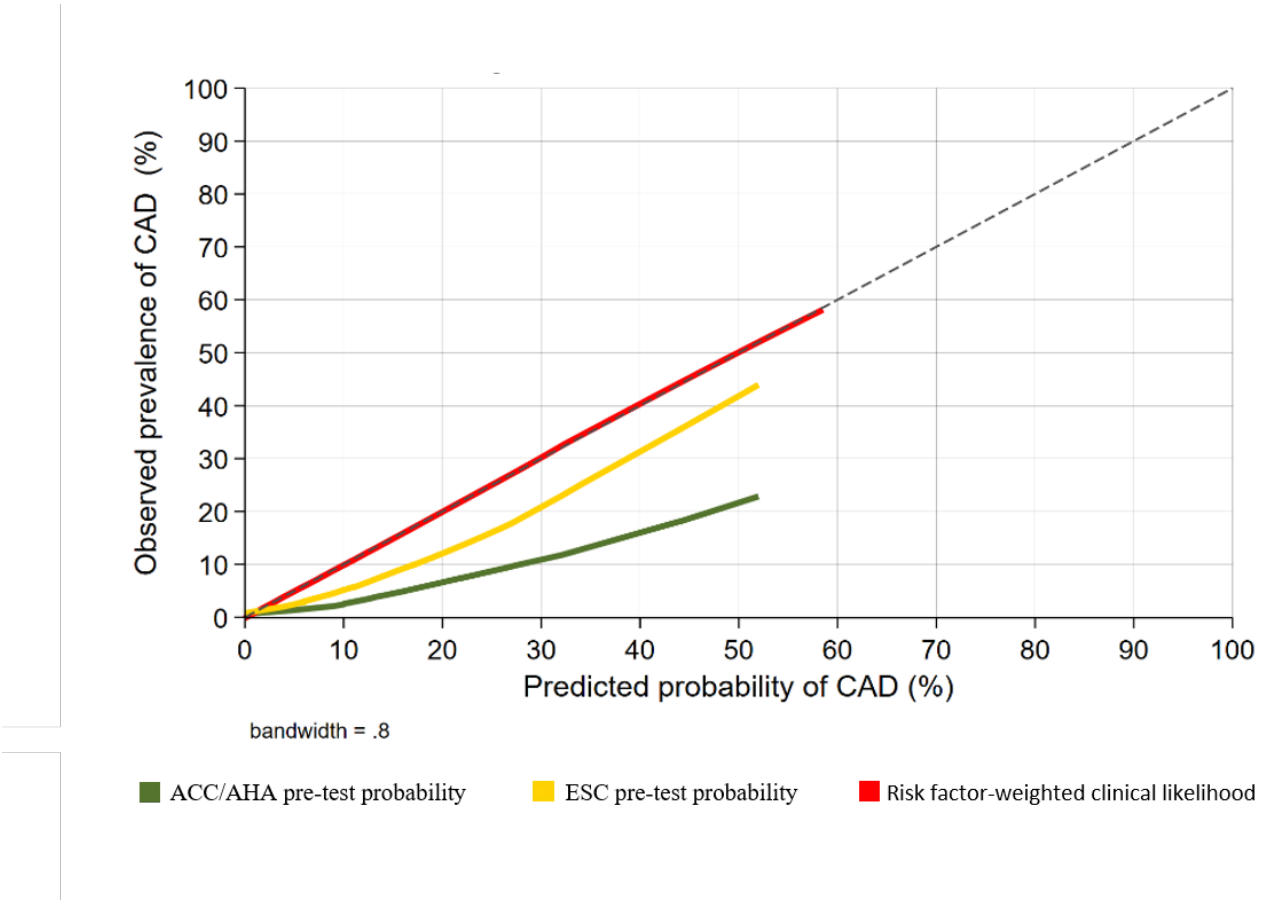
Age	Dyspnea		Chest pain	
	Women	Men	Women	Men
30-39	6	4	1	2
40-49	1	5	2	6
50-59	2	9	3	11
60-69	4	16	6	17
> 70	7	24	10	24

B) ACC/AHA guideline model

Age	Dyspnea		Chest pain	
	Women	Men	Women	Men
30-39	3	0	< 5	< 4
40-49	3	12	< 10	< 22
50-59	9	20	< 13	< 32
60-69	14	27	< 16	< 44
> 70	12	32	< 27	< 52

Abbreviations: American Heart Association/ American College of Cardiology (AHA/ACC) and Coronary artery disease (CAD).

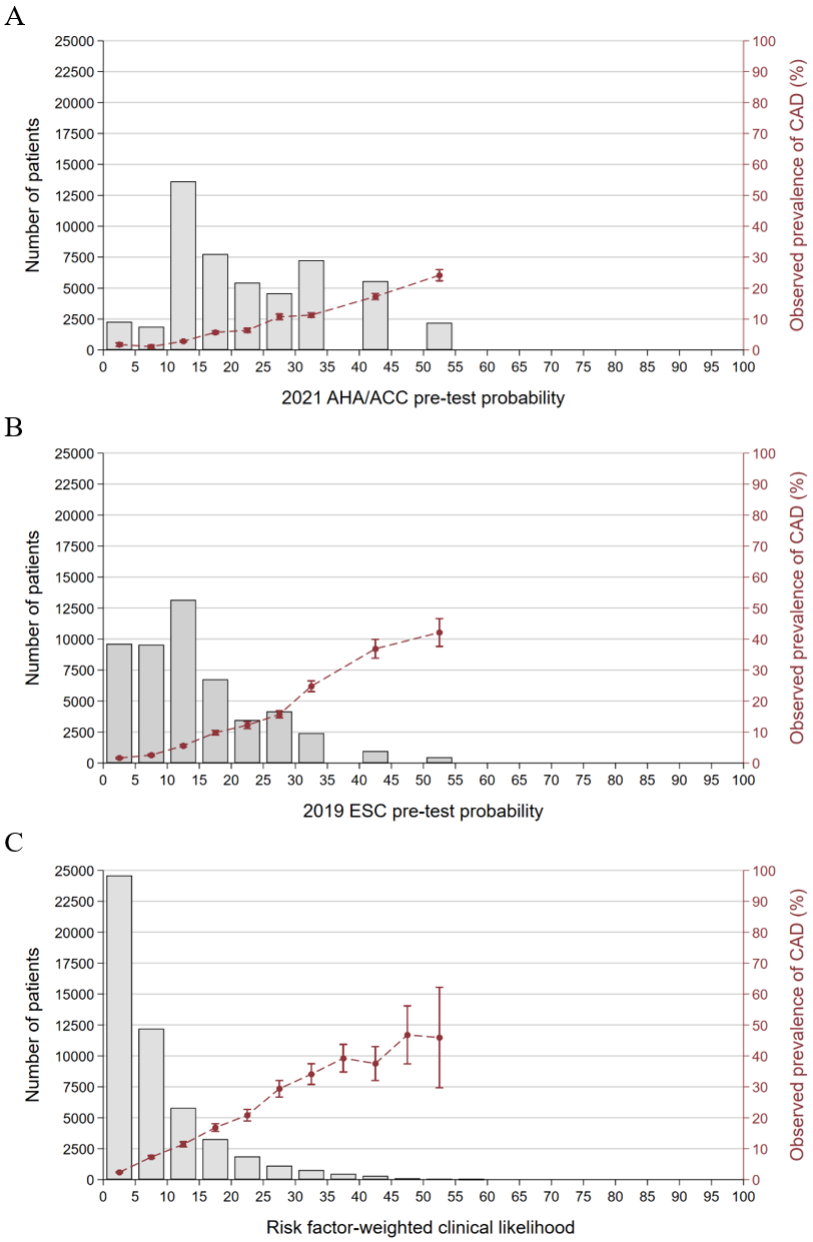
Figure S3. Calibration plot of the mean predicted probability and the mean observed proportion of minimal risk with flexible calibration (Loess bandwidth 0.8) were evaluated. Analysis of the "calibration-in-the-large" and "calibration slope" were done for each model. Perfect predictions should be on 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").



Model	Calibration-in-the-large	Slope
AHA/ACC-PTP	-1.30 (95% CI, -1.33 to -1.27)	1.05 (95% CI, 1.00 to 1.10)
ESC-PTP	-0.63 (95% CI, -0.60 to -0.66)	1.12 (95% CI, 1.08 to 1.17)
RF-CL	-0.02 (95% CI, 0.01 to -0.05)	1.01 (95% CI, 0.98 to 1.05)

Abbreviations: American Heart Association/ American College of Cardiology (AHA/ACC), Coronary artery disease (CAD), European Society of Cardiology (ESC), Pre-test probability (PTP) and Risk factor-weighted clinical likelihood (RF-CL).

Figure S4. The number of patients (bars) and the prevalence of CAD with 95% confidence intervals (red line) for A) the 2021 AHA/ACC Guideline for the Evaluation and Diagnosis of Chest Pain, B) 2019 European Society of Cardiology guidelines for the diagnosis and management of chronic coronary syndromes and C) the Risk factor-weighted clinical likelihood (RF-CL) model.



The figures show that the RF-CL model reclassify more patients to low likelihood of CAD and that the observed prevalence of CAD remain very low in these categories. Confidence intervals are shown only in groups with >10 patients.

Abbreviations: American Heart Association/ American College of Cardiology (AHA/ACC), Coronary artery disease (CAD) and European Society of Cardiology (ESC).

Figure S5. Reclassification tables including calculation of net reclassification improvement for A) AHA/ACC-PTP versus ESC-PTP and B) ESC-PTP versus RF-CL.

A

Reclassification of patients with versus without obstructive CAD
AHA/ACC-PTP versus ESC-PTP

Numbers of patients and prevalence of CAD

		ESC-PTP				
		≤ 5%	5 - 15%	15 - 50%	> 50%	Total
AHA/ACC-PTP	≤ 5%	2,282	0	0	0	2,282
	5 - 15%	5,538	9,962	0	0	15,500
	15 - 50%	1,798	12,747	16,044	0	30,589
	> 50%	0	0	1,720	470	2,190
Total		9,618	22,709	17,764	470	50,561

Numbers of patients with obstructive CAD

		ESC-PTP				
		≤ 5%	5 - 15%	15 - 50%	> 50%	Total
AHA/ACC-PTP	≤ 5%	40	0	0	0	40
	5 - 15%	63	345	0	0	408
	15 - 50%	56	637	2,364	0	3,057
	> 50%	0	0	331	198	529
Total		159	982	2,695	198	4,034

Numbers of patients without obstructive CAD

		ESC-PTP				
		≤ 5%	5 - 15%	15 - 50%	> 50%	Total
AHA/ACC-PTP	≤ 5%	2,242	0	0	0	2,242
	5 - 15%	5,475	9,617	0	0	15,092
	15 - 50%	1,742	12,110	13,680	0	27,532
	> 50%	0	0	1,389	272	1,661
Total		9,459	21,727	15,069	272	46,527

Net reclassification index

Net reclassification index = 0.176 (CI95% 0.159-0.193)

B

Reclassification of patients with versus without obstructive CAD
ESC-PTP versus RF-CL

Numbers of patients and prevalence of CAD

		RF-CL				
		≤ 5%	5 - 15%	15 - 50%	> 50%	Total
ESC-PTP	≤ 5%	9,214	372	32	0	9,618
	5 - 15%	14,814	7,794	101	0	22,709
	15 - 50%	562	9,843	7,358	1	17,764
	> 50%	0	0	430	40	470
Total		24,590	18,009	7,921	41	50,561

Numbers of patients with obstructive CAD

		RF-CL				
		≤ 5%	5 - 15%	15 - 50%	> 50%	Total
ESC-PTP	≤ 5%	130	28	1	0	159
	5 - 15%	428	545	9	0	982
	15 - 50%	24	978	1,692	1	2,695
	> 50%	0	0	180	18	198
Total		582	1,551	1,882	19	4,034

Numbers of patients without obstructive CAD

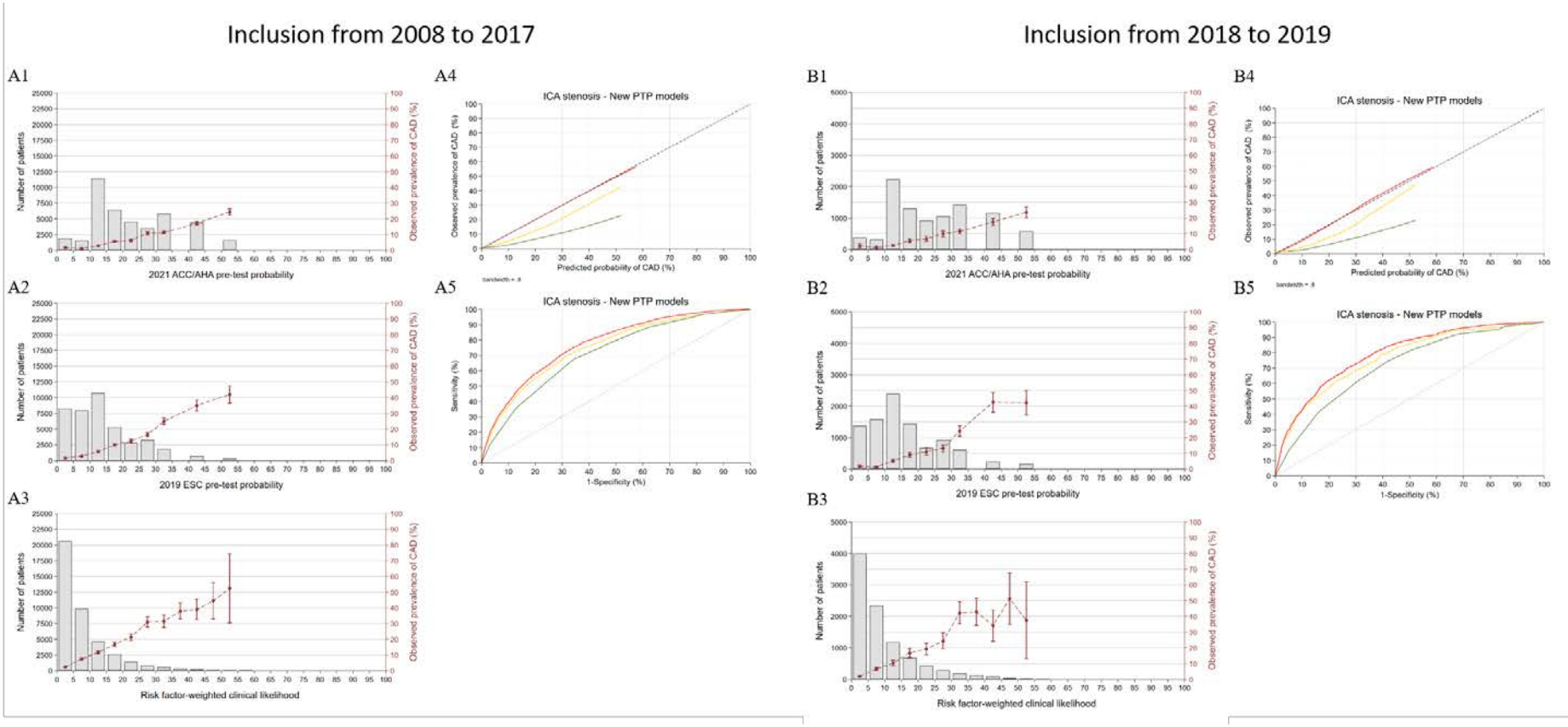
		RF-CL				
		≤ 5%	5 - 15%	15 - 50%	> 50%	Total
ESC-PTP	≤ 5%	9,084	344	31	0	9,459
	5 - 15%	14,386	7,249	92	0	21,727
	15 - 50%	538	8,865	5,666	0	15,069
	>5 0%	0	0	250	22	272
Total		24,008	16,458	6,039	22	46,527

Net reclassification improvement

Net reclassification index = 0.117 (CI95% 0.096-0.138)

Abbreviations: American Heart Association/ American College of Cardiology (AHA/ACC), Coronary artery disease (CAD), European Society of Cardiology (ESC), Pre-test probability (PTP) and Risk factor-weighted clinical likelihood (RF-CL).

Figure S6. Data presented is stratified for early inclusion period (2008 to 2017) vs. late inclusion period (2018-2019) demonstrating stable diagnostic performance when evaluated with reclassification bar graphs, calibration plot and receiver-operator curve for the three models. The reference standard used is ICA. Patients included in the early inclusion period was previously used as training cohort for the development of the Risk factor-weighted clinical likelihood model but subsequently validation in the late inclusion period showed stable performance.



Abbreviations: American Heart Association/ American College of Cardiology (AHA/ACC), Coronary artery disease (CAD), European Society of Cardiology (ESC), Invasive coronary angiography (ICA), Pre-test probability (PTP) and Risk factor-weighted clinical likelihood (RF-CL).