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External validation of novel clinical likelihood models to predict obstructive coronary artery disease and prognosis

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ABSTRACT

Objectives The risk factor-weighted and coronary artery calcium score-weighted clinical likelihood (RF-CL and CACS-CL, respectively) models improve discrimination of patients with suspected obstructive coronary artery disease (CAD). However, external validation is warranted. Compared to the 2019 European Society of Cardiology pretest probability (ESC-PTP) model, the aims were (1) to validate the RF-CL and CACS-CL models for identification of obstructive CAD and revascularisation, and (2) to investigate prognosis by CL thresholds.

Methods Stable de novo chest pain patients (n=1585) undergoing coronary CT angiography (CTA) were investigated. Obstructive CAD was defined as >70% diameter stenosis in a major epicardial vessel on CTA. Decision of revascularisation within 120 days was based on onsite judgement. The endpoint was non-fatal myocardial infarction or cardiovascular death. The ESC-PTP was calculated based on age, sex and symptom typicality, the RF-CL additionally included number of risk factors, and the CACS-CL incorporated CACS to the RF-CL.

Results Obstructive CAD was present in 386/1585 (24.4%) patients, and 91/1585 (5.7%) patients underwent revascularisation. Both the RF-CL and CACS-CL classified more patients to very-low CL (<5%) of obstructive CAD compared with the ESC-PTP model (41.4% and 52.2% vs 19.2%, p<0.001). In very-low CL patients, obstructive CAD and revascularisation prevalences (≤6% and <1%) remained similar combined with low event risk during 5.0 years follow-up.

Conclusion In an external validation cohort, the novel RF-CL and CACS-CL models improve categorisation to a very-low CL group with preserved prevalences of obstructive CAD, revascularisation and favourable prognosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Estimation of pretest probability (PTP) is recommended to guide referral for non-invasive testing and treatment decisions in patients with symptoms suggestive of obstructive coronary artery disease (CAD).

⇒ Novel risk factor-weighted and coronary artery calcium score-weighted clinical likelihood models (ie, the RF-CL and CACS-CL models, respectively) for patient-specific PTP estimation have been proposed, yielding superior discrimination of obstructive CAD compared with a currently endorsed basic PTP model. However, as patient demographics and CAD prevalences vary nationally, further external validation is warranted.

WHAT THIS STUDY ADDS

⇒ In an external validation cohort, the novel RF-CL and CACS-CL models improve categorisation to a very-low CL group with preserved low prevalences of obstructive CAD, revascularisation and overall favourable prognosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Yielding superior discrimination in multiple external validation cohorts, the RF-CL and CACS-CL models should be preferred for PTP assessment of patients with de novo chest pain to improve decisions on downstream test referral and deferral.

INTRODUCTION

Estimation of pretest probability (PTP) is recommended to guide referral for non-invasive testing and treatment decisions in patients with symptoms suggestive of obstructive coronary artery disease (CAD).[1 2] Additionally, post-test probabilities following non-invasive diagnostic tests are estimated by combining PTP estimates with likelihood ratios.[3] Hence, PTP model precision is a major concern to ensure optimal patient management.

Classically, PTP models stratify patients with de novo chest pain by sex, age and type of chest pain symptoms.[1] Further, the incorporation of cardiovascular risk factors and coronary artery calcium score (CACS) is acknowledged to modify patient-specific clinical likelihood (CL).[1] However, a clinically feasible and validated tool to estimate the CL of obstructive CAD was recognised as a 'gap in evidence' by the 2019 European Society of Cardiology (ESC) guidelines on chronic coronary syndrome.[1]

Recently, simple and clinically useful tools for patient-specific CL estimation were proposed.[4] Validated in North-American, Danish and Chinese cohorts, the risk factor-weighted and CACS-weighted CL models (RF-CL and CACS-CL, respectively) show improved prediction and discrimination of both obstructive CAD and future cardiovascular events in patients with suspected obstructive CAD.[4–6] However, as patient demographics and CAD prevalences vary nationally,[7] further external validation is warranted to ensure general feasibility.

Thus, using the Scottish CT of the HEART (SCOT-HEART) trial[8 9] and compared with the ESC-PTP model,[1] we aimed to externally validate the RF-CL and CACS-CL models to discriminate obstructive CAD and predict prognosis.

METHODS

Patients and study design

This study included data from the SCOT-HEART trial.[8 9] Patients were randomly allocated to either (1) standard care or (2) standard care with additional CACS and coronary CT angiography (CTA) (CTA arm). Similar to a previous study that proposes a novel exercise electrocardiography-weighted CL model,[10] the current validation study was restricted to patients without known CAD allocated to the CTA arm (n=1796) with CACS and CTA data available (final population; n=1585).

In short, the proportion of patient classified to very low (≤5%), low (5–15) or moderate/high (>15%) CL categories were compared between the ESC-PTP model, the RF-CL model and the CACS-CL models, respectively. Second, calibration and discrimination were investigated against obstructive CAD defined by coronary CTA and revascularisation within 120 days following coronary CTA. Finally, prognosis was investigated according to CL classification.

Definitions of variables

The ESC-PTP variables included sex, age and type of chest symptoms at referral, the latter further categorised as either typical, atypical and non-anginal chest pain. Typical chest pain covered (1) discomfort in the chest, neck, jaw, shoulder or arm of constricting character; (2) symptoms provoked by exertion or emotional stress; and (3) symptoms relieved by rest or nitroglycerine. Atypical chest pain was defined as meeting two out of three criteria for typical chest pain. Non-anginal chest pain encompassed all other chest pain symptoms.

Risk factors included in the RF-CL were family history of ischaemic heart disease, smoking, dyslipidaemia, hypertension and diabetes. The definition of family history included first-degree relatives with early signs of ischaemic heart disease, men <55 years of age and women <65 years of age. Smoking was defined as current smoker or a history of smoking. Dyslipidaemia, hypertension and diabetes were defined as either diagnosed by a physician or if receiving medical treatment for these conditions.

Table 1 Baseline characteristics

	n=1585
Characteristics	
Male	859 (54.2)
Age	
Mean age (years)	57.2±9.5
<50	345 (21.8)
50–60	547 (34.5)
60–70	541 (34.1)
≥70	152 (9.6)
Risk factors	
Family history of early CAD	686 (43.3)
Smoking history	813 (51.3)
Dyslipidaemia	645 (40.7)
Hypertension	532 (33.6)
Diabetes	151 (9.5)
Cardiac symptoms at referral	
Typical chest pain	555 (35.0)
Atypical chest pain	386 (24.4)
Non-specific chest pain	644 (40.6)
Disease severity by coronary CTA	
CACS (AU)	11 (0–158)
No or non-obstructive CAD	1199 (75.6)
Obstructive CAD	386 (24.4)
Invasive coronary angiography	
Within 120 days following coronary CTA	
No revascularisation	1494 (94.3)
Revascularisation	91 (5.7)

Values are n (%), mean±SD, or median (IQR).
AU, Agatston units; CACS, coronary artery calcium score; CAD, coronary artery disease; CTA, CT angiography.

Additionally, information was collected from the national registers for diagnosis codes or registered prescribed medicine for the specific conditions. CACS was calculated based on non-contrast enhanced CT scan using the Agatston method.

Calculation of CL models

The ECT-PTP model was calculated from sex, age and type of chest pain as recommended in the 2019 ESC guidelines on chronic coronary syndrome.[1] The RF-CL was additionally calculated from the number of risk factors ranging from 0 to 5 (see above),[4] and the CACS-CL incorporated CACS to the RF-CL model.[4]

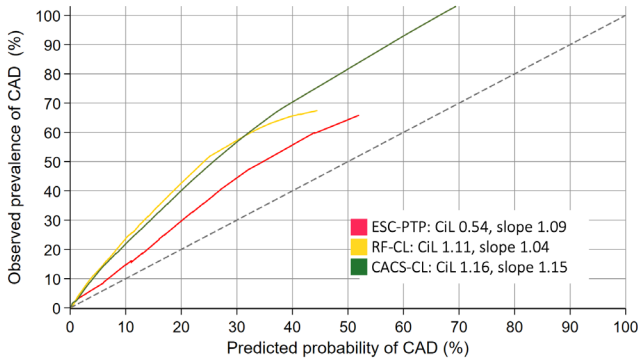
All models were divided into groups of very-low (≤5%), low (>5%–15%) and moderate-high (>15%) likelihood of obstructive CAD.

Reference standards and clinical endpoint

Obstructive CAD was defined as >70% diameter stenosis in a major epicardial vessel on CTA as previously reported.[8]

Diagnostic performance against obstructive CAD defined by coronary CTA

A



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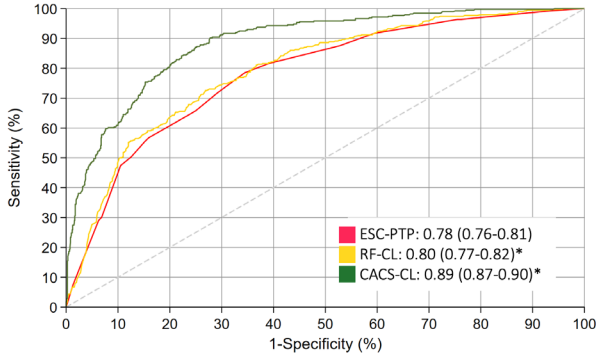


C Distribution of patients to CAD prevalence by CL categories

CAD prevalence	<5%	5-15%	≥15%
ESC-PTP	14/305 4.6%	69/564 12.2%	303/716 42.3%
RF-CL	44/656 6.4%	118/523 22.9%*	224/406 55.2%*
CACS CL	29/828 3.5%	71/290 24.5%*	286/467 61.2%*

D Diagnostic performance according to 5% cut-off

Diagnostic accuracy	Sensitivity	Specificity	PPV	NPV
ESC-PTP	96.4% (94.0-98.0)	24.3% (21.9-26.8)	29.1 % (26.6-31.6)	95.4 % (92.4-97.5)
RF-CL	88.6 % (85.0-91.6)*	51.0 % (48.2-53.9)*	36.8 % (33.7-40.0)*	93.3 % (91.1-95.1)
CACS CL	92.5 % (89.4-94.9)*	66.6% (63.9-69.3)*	47.2 % (43.6-50.8)*	96.5 %(95.0-97.6)

Figure 1 Diagnostic performance of the ESC-PTP, RF-CL and CACS-CL models against obstructive CAD by coronary CTA (n=1585). (A) All models underestimated the probability of obstructive CAD with superior prediction by the ESC-PTP compared with the RF-CL and CACS-CL models. (B) Receiver-operating characteristic curves show good and superior discrimination of the RF-CL and CACS-CL models compared with the ESC-PTP model. (C) The distribution of patients according to clinical likelihood cut-offs and the corresponding prevalence of obstructive CAD illustrate the reclassification ability of the RF-CL and CACS-CL models. (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 all models. *denotes <0.05 for comparison to the ESC-PTP. CACS-CL, coronary artery calcium score-weighted clinical likelihood; CAD, coronary artery disease; CiL, calibration in the large; CTA, CT tomography angiography; ESC, European Society of Cardiology; PTP, pretest probability; RF-CL, risk factor-weighted clinical likelihood.

Second, revascularisation within 120 days after coronary CTA was used as reference standard.

The clinical endpoint was non-fatal myocardial infarction and cardiovascular death at 5 years.

Statistical analyses

Variables are expressed as mean±SD or median (range), categorical variables reported as frequencies (percentages). The RF-CL and CACS-CL models were compared with the ESC-PTP model.

Discrimination was assessed using the area under the receiver operating characteristic curve (ROC-AUC), and AUCs were compared using the DeLong algorithm. Additionally, diagnostic performance was evaluated by sensitivity, specificity, positive and negative predictive values (NPV) using a ≤5% CL cut-off. Comparison of sensitivities and specificities was tested using McNemar's test and a weighted generalised score statistics for comparison of predictive values of diagnostic tests.

For time-to-event analyses, Cox-regression assumptions were met and HRs were calculated. The cumulative incidence of the primary outcome, non-fatal myocardial infarction and cardiovascular death, was estimated using the Aalen-Johansen method with non-cardiovascular death as competing risk, while the Kaplan-Meier method was used for non-fatal myocardial infarction and all-cause death.

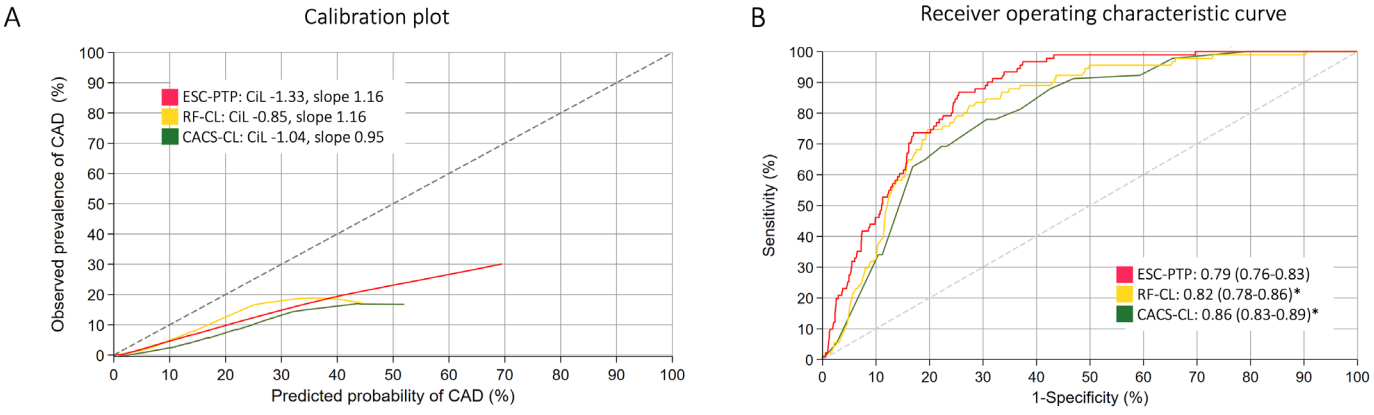
RESULTS

In total, 1585 patients were available for statistical analyses. Patient demographics and CAD characteristics are outlined in table 1. Obstructive CAD was present in 386/1585 (24.4%) patients, and 91/1585 (5.7%) patients underwent revascularisation within 120 days following coronary CTA.

Calibration of the CL models

Calibration of the ESC-PTP, RF-CL and CACS-CL models against obstructive CAD on coronary CTA is shown in figure 1A. Overall, all models underestimated the probability of obstructive CAD defined by coronary CTA which was more pronounced for the RF-CL and CACS-CL models compared with the ESC-PTP model.

Diagnostic performance against revascularization within 120 days following CTA



C Distribution of patients to revascularization prevalence by CL categories

Revascularization prevalence	<5%	5-15%	≥15%
ESC-PTP	0/305 0.0%	11/564 2.0%	80/636 11.2%
RF-CL	4/656 0.6%	18/523 3.4%*	69/406 17.0%*
CACS CL	1/828 0.1%	11/290 3.8%*	79/467 16.9%*

D Diagnostic performance according to 5% cut-off

Diagnostic accuracy	Sensitivity	Specificity	PPV	NPV
ESC-PTP	100% (96.0-100)	20.4% (18.4-22.5)	7.1% (5.8-8.7)	100% (98.8-100)
RF-CL	95.6% (89.1-98.8)*	43.6% (41.1-46.2)*	9.4% (7.6-11.4)	99.4% (98.4-99.8)*
CACS CL	98.9% (94.0-100)	55.4% (52.8-57.9)*	11.9% (9.7-14.4)*	99.9% (99.3-100)

Figure 2 Diagnostic performance of the ESC-PTP, RF-CL and CACS-CL models against revascularisation within 120 days following CTA (n=1585). (A) All models overestimated the probability of revascularisation within 120 days following coronary CTA. (B) Receiver-operating characteristic curves show good and superior discrimination of the RF-CL and CACS-CL models compared with the ESC-PTP model. (C) The distribution of patients according to clinical likelihood cut-offs and the corresponding prevalence of revascularisation illustrate the reclassification ability of the RF-CL and CACS-CL models. (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 all models. *denotes <0.05 for comparison to the ESC-PTP. CACS-CL, coronary artery calcium score-weighted clinical likelihood; CAD, coronary artery disease; CiL, calibration in the large; CTA, CT angiography; ESC, European Society of Cardiology; PTP, pretest probability; RF-CL, risk factor-weighted clinical likelihood.

Calibration of the ESC-PTP, RF-CL and CACS-CL models against revascularisation within 120 days following coronary CTA is shown in figure 2A. Overall, all models overestimated the probability of revascularisation, with the RF-CL model showing the smallest degree of revascularisation probability overestimation. In general, all models showed increasing probability overestimation with increasing CL.

Discrimination of the CL models

ROC-AUC curves for the discrimination of obstructive CAD by the ESC-PTP, RF-CL and CACS-CL models are shown in figure 1B. Compared with the ESC-PTP model, both the RF-CL and CACS-CL models showed superior discrimination (AUC 0.78 (0.76 to 0.81) vs 0.80 (0.77 to 0.82), p<0.01, and 0.89 (0.87 to 0.90), p<0.001, respectively). Compared with the RF-CL model, the CACS-CL model showed improved discrimination (p<0.001).

ROC-AUC curves for the discrimination of revascularisation within 120 days following coronary CTA by the ESC-PTP, RF-CL and CACS-CL models are shown in figure 2B. Compared with the ESC-PTP model, both the RF-CL and CACS-CL models showed superior discrimination (0.79 (0.76 to 0.83) vs 0.82 (0.78 to 0.86), p<0.05, and 0.86 (0.83 to 0.89), p<0.001, respectively). Compared with the RF-CL model, the CACS-CL model showed improved discrimination (p<0.001).

Reclassification of the CL models

Patient distribution and obstructive CAD prevalence at coronary CTA for the ESC-PTP, RF-CL and CACS-CL models are shown in figure 1C and online supplemental table 1). Compared with the ESC-PTP model, both the RF-CL and CACS-CL models classified more patients to a very-low CL group (CL ≤5%) with preserved prevalences of obstructive CAD. Using a ≤5% cut-off for obstructive CAD rule-out, both the RF-CL and CACS-CL models showed lower sensitivities compared with the ESC-PTP model (figure 1D). Overall, the RF-CL and CACS-CL models showed higher specificities compared with the ESC-PTP model with all models reporting high NPVs between 93% and 97%.

Patient distribution and prevalence of revascularisation within 120 days following coronary CTA for the ESC-PTP, RF-CL and CACS-CL models are shown in figure 2C and online supplemental table 1). Compared with the ESC-PTP model, both the RF-CL and CACS-CL models classified more patients to a very-low CL group (CL ≤5%) with preserved low prevalences of revascularisation. Using a ≤5% CL cut-off for revascularisation rule-out, the RF-CL model showed lower sensitivity compared with the ESC-PTP model while the CACS-CL model had similar sensitivity (figure 2D). Overall, the RF-CL and CACS-CL models showed higher specificities compared with the ESC-PTP model with all models reporting high NPVs between 99% and 100%.

CL models and prognosis

The clinical endpoint of non-fatal myocardial infarction and cardiovascular death occurred in 17/1585 (1.1%) patients. Overall, event rates increased with increasing ESC-PTP, RF-CL and CACS-CL (table 2 and figure 3). Importantly, patients with very-low CL across all CL models had very low event rates ≤0.1%, and no event rate differences were observed for patients categorised with very-low, low or intermediate/high CL between the ESC-PTP, RF-CL and CACS-CL models, respectively.

Comparing the models by Harrell's C and Somers' D, the RF-CL and CACS-CL models were superior for prediction of the clinical endpoint compared with the ESC-PTP model (online supplemental table 2).

Table 2 Annular event rates (ER) and HRs including 95% CIs against the clinical endpoint of non-fatal myocardial infarction and cardiovascular death stratified by ESC-PTP, RF-CL and CACS-CL groups, respectively, and risk statistics

	CL groups		
	≤5%	5-≤15%	>15%
ESC-PTP			
ER	0.0%	0.3% (0.1 to 0.7)	0.4% (0.2 to 0.8)
HR	Ref.	1.6 (0.2 to 5.3), p=0.64	2.2 (0.8 to 6.9), p<0.01
RF-CL			
ER	0.1% (0.1 to 0.3)	0.4% (0.2 to 0.8)	0.6% (0.3 to 1.2)
HR	Ref.	4.2 (0.8 to 20.0), p=0.05	5.9 (1.22 to 28.2), p=0.02
CACS-CL			
ER	0.1% (0.1 to 0.2)	0.6% (0.3 to 1.4)	0.7% (0.3 to 1.1)
HR	Ref.	8.4 (1.7 to 41.8), p=0.01	7.9 (1.7 to 37.1), p=0.01

CACS-CL, coronary artery calcium score-weighted clinical likelihood; CL, clinical likelihood; ESC, European Society of Cardiology; PTP, pretest probability; RF-CL, risk factor-weighted clinical likelihood.

DISCUSSION

In this large-scale external validation of the RF-CL and CACS-CL models, both models showed impaired calibration but superior discrimination against obstructive CAD on coronary CTA compared with the currently guideline-endorsed ESC-PTP model. Importantly, model calibration improved for the RF-CL and CACS-CL models against a reference standard of revascularisation. Compared with the ESC-PTP model, more patients were downclassified to a very-low CL group with preserved prevalences of obstructive CAD and revascularisation with overall favourable prognosis.

CL estimation in chronic coronary syndrome

Recognised as a gap in evidence by the 2019 ESC guidelines on chronic coronary syndrome,[1] the RF-CL and CACS-CL models were developed as tabulated, simple and clinically useful tools for improved prediction of obstructive CAD in patients with de novo chest pain.[4] Other models have been proposed, including the CAD consortium (CADC) clinical and CADC+CACS models[11] but their clinical utility is limited by the need for online calculation.

In general, both the RF-CL and CACS-CL models improved discrimination of obstructive CAD compared with the currently recommended ESC-PTP model (figure 1B).[1] Importantly, the RF-CL and CADC-CL models classified more patients (41.4% and 52.2%, respectively) at very-low CL of obstructive CAD (≤5%), where neither European nor North-American guidelines recommend downstream testing.[1 2] Against a reference standard of obstructive CAD, sensitivity was slightly impaired for the RF-CL and CACS-CL models compared with the ESC-PTP model but across all CL tables, the NPVs remained high (93% to 97%) and obstructive CAD prevalences similar (figure 1C,D). In alignment with the original derivation study,[4] the CACS-CL model also reduced the number of patients with low (5%–15%) CL of obstructive CAD in whom diagnostic testing can be considered without clear guideline recommendations.[1]

In patients with moderate/severe myocardial ischemia but without high-risk CAD by coronary CTA, the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches authors reported similar prognosis but improved quality of life in patients undergoing revascularisation compared with patients allocated to guideline-directed medical therapy.[12 13] Thus, one could argue that prognostic CAD should be ruled out by coronary CTA, and referral for invasive coronary angiography (ICA) and potentially revascularisation should be restricted to patients with medically refractory symptoms. CACS is known to be a very strong predictor of obstructive CAD,[14] and discrimination of obstructive coronary lesions improves by the CACS-CL compared with models without CACS utilisation (figure 1).[4 5] In general, CACS only represents a surrogate for calcified coronary arteriosclerosis and is not a diagnostic test, and the utility of CACS as a tool to stratify patients is debatable.

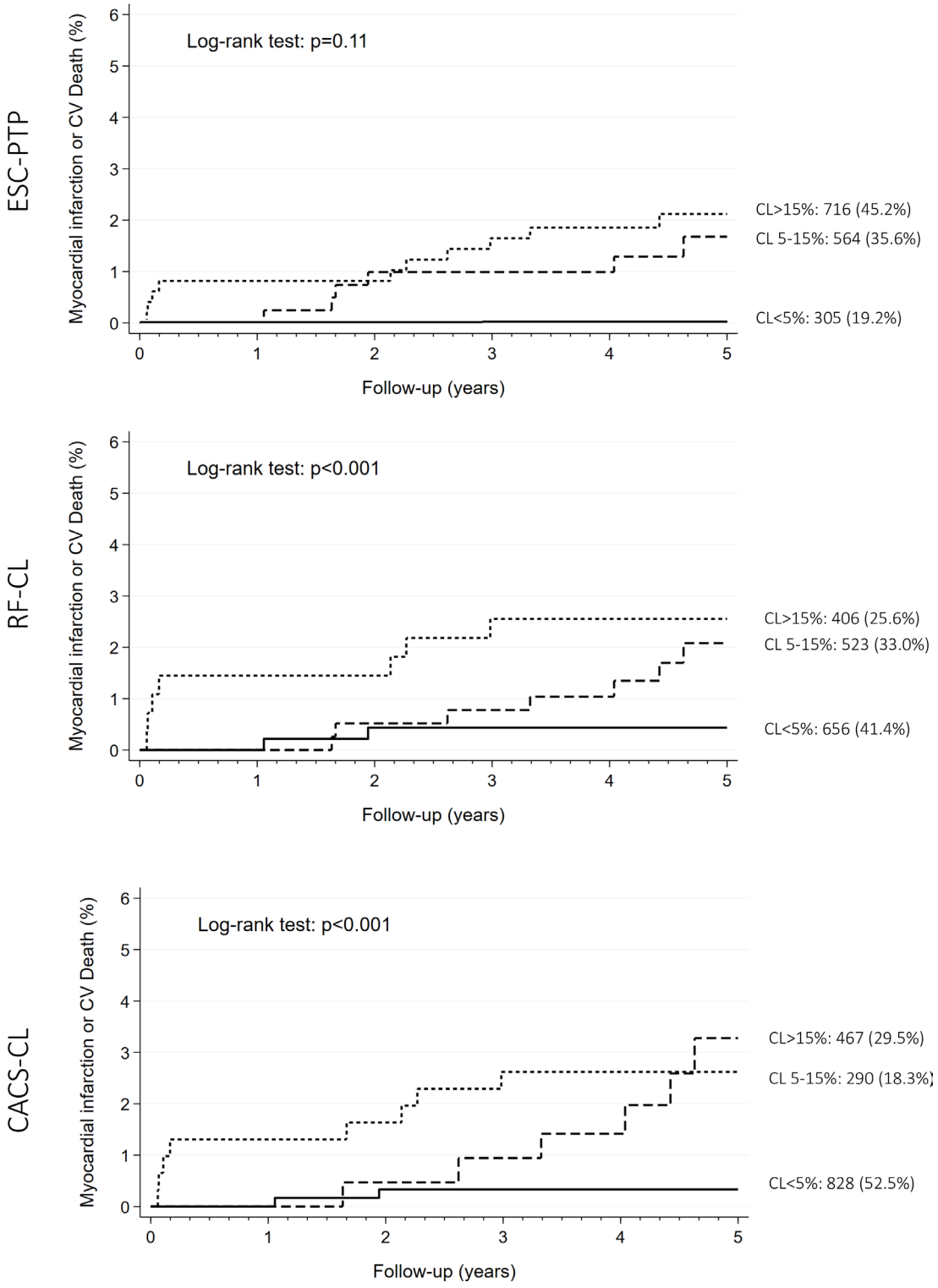


Figure 3 Kaplan-Maier curves against the clinical endpoint of non-fatal myocardial infarction and cardiovascular death stratified by ESC-PTP, RF-CL and CACS-CL groups. CACS-CL, coronary artery calcium score-weighted clinical likelihood; CAD, coronary artery disease; CiL, calibration in the large; CTA, CT angiography; ESC, European Society of Cardiology; PTP, pretest probability; RF-CL, risk factor-weighted clinical likelihood.

Definition of obstructive CAD

In our study, the ESC-PTP underestimated the observed prevalence of obstructive CAD at coronary CTA less than the RF-CL and CACS-CL models (figure 1A). However, model calibration improved across all risk tables against revascularisation (figure 2A). Based on the 2019 ESC guidelines on chronic coronary syndrome, the ESC-PTP model reflects the probability of obstructive CAD in a pooled analysis from three studies: the PROMISE trial

(n=4415),[15] the CONFIRM registry (n=8106)[16] and a study by Reeh *et al* (n=3291).[17] In the PROMISE and CONFIRM populations, coronary CTA was used as reference standard of obstructive CAD, while Reeh *et al* used a mixed endpoint of either non-invasive or invasive tests. As (1) the RF-CL and CACS-CL models were derived against ICA as reference for obstructive CAD,[4] and (2) coronary CTA overestimates lesion severity by invasive measures,[18] the improved calibration of the RF-CL and CACS-CL models against revascularisation compared with obstructive CAD at coronary CTA is expected. Importantly, the calibration of CL models is impacted by the chosen reference standard where CL estimates contribute to PTP assessment after advanced non-invasive diagnostic testing.[3] As abnormal non-invasive tests guide potential revascularisation, CL models should be calibrated against ICA, alternatively inducible myocardial ischaemia[19] and ultimately revascularisation.[4 20]

Prognosis in chronic coronary syndrome

In our study, the CACS-CL model was superior for the prediction of the clinical endpoint compared with the ESC-PTP (online supplemental table 2). Overall, all CL models found patients with very-low CL to have a 5-year absolute risk <1.0% of myocardial infarction and cardiovascular death (figure 3). Importantly, the ESC-PTP, RF-CL and CACS-CL models are all calibrated against obstructive CAD whereas myocardial infarction also occurs in non-obstructive lesions in 1 of 10 patients.[21] Patients with non-obstructive lesions are presumably missed by models not integrating CACS though CACS only surrogates coronary atherosclerosis by outlining coronary calcification. However, event rates of the clinical endpoint were similar for low and moderate/high CL patients by the CACS-CL model (table 2).

Overall, our findings are consistent with previous studies, and the improved very-low CL categorisation by the RF-CL and CACS-CL models seem safe across various study cohorts.[6]

Limitations

Our cohort consisted exclusively of Caucasian patients, and results should be extrapolated carefully. All patients had chest pain but dyspnoea was not recorded in SCOT-HEART and CL estimates are solely based on chest pain typicality. Our cohort underwent coronary CTA which improves prognosis by early initiation of guideline-directed medical therapy and this could impact subsequent cardiac outcomes.[9]

CONCLUSION

In patients with de novo chest pain from an external validation cohort, the novel RF-CL and CACS-CL models improve categorisation to a very-low CL group with preserved prevalence of obstructive CAD, low prevalence of revascularisation and overall favourable prognosis.

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Contributors LDR, SW and MB designed the study. DEN and MCW provided data for analyses. LDR, SW, SES and JND analysed the data. All authors interpreted data and drafted the manuscript. LDR acts as guarantor.

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Competing interests MB acknowledge support from Acarix in form of an institutional research grant. MB discloses advisory board participation for NOVO Nordisk, Astra-Zeneca, Bayer, Boehringer Ingelheim, Novartis, Sanofi, and Acarix outside of submitted work. MCW has given talks for Canon Medical Systems, Siemens Healthineers and Novartis. DEN is on the Editorial Board and is Deputy Editor of Heart. The remaining authors have nothing to disclose.

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

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by University of Edinburgh. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Not applicable.

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