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Standard clinical and stress electrocardiogram variables to exclude left main and left main-equivalent disease: the MASTER study

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Abstract

Background and Aims A simple diagnostic method able to reliably exclude left main (LM) coronary artery disease (CAD) or LMCAD-equivalent would expand implementation of an initial non-invasive strategy in patients with chronic coronary syndrome (CCS). This study assessed the diagnostic utility of an approach using clinical and ECG stress testing (EST) variables in excluding LMCAD/LMCAD-equivalent in CCS patients.

Methods In a multicentre case-control study, CCS patients undergoing invasive coronary angiography (CAG) after a maximal EST were evaluated. Cases were patients with angiographic ≥ 50% LM stenosis or ≥70% stenosis of both proximal left anterior descending and proximal circumflex arteries, matched with similar patients without them (controls) in a 1:3 ratio. A risk model developed through logistic regression was internally and externally validated.

Results Three hundred and thirty-five cases were matched with 797 controls. The model area under the curve (AUC) was .78. Assuming LMCAD prevalence of 5% and a misclassification cost ratio of 1:100 (ratio of cost of performing CAG in a control to cost of not performing CAG in a case), negative predictive value was 98.2%. Thus, CAG could be safely avoided in 41% of patients, missing one LMCAD/LMCAD-equivalent diagnosis for every 58 CAGs safely spared in patients without them.

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Conclusions Among CCS patients, LMCAD/LMCAD-equivalent can be excluded with high negative predictive value through a model based on clinical and EST parameters, allowing initial non-invasive management of most patients able to exercise. This approach is potentially useful particularly in communities where access to computed tomography coronary angiography is limited.

Structured Graphical Abstract

Key Question

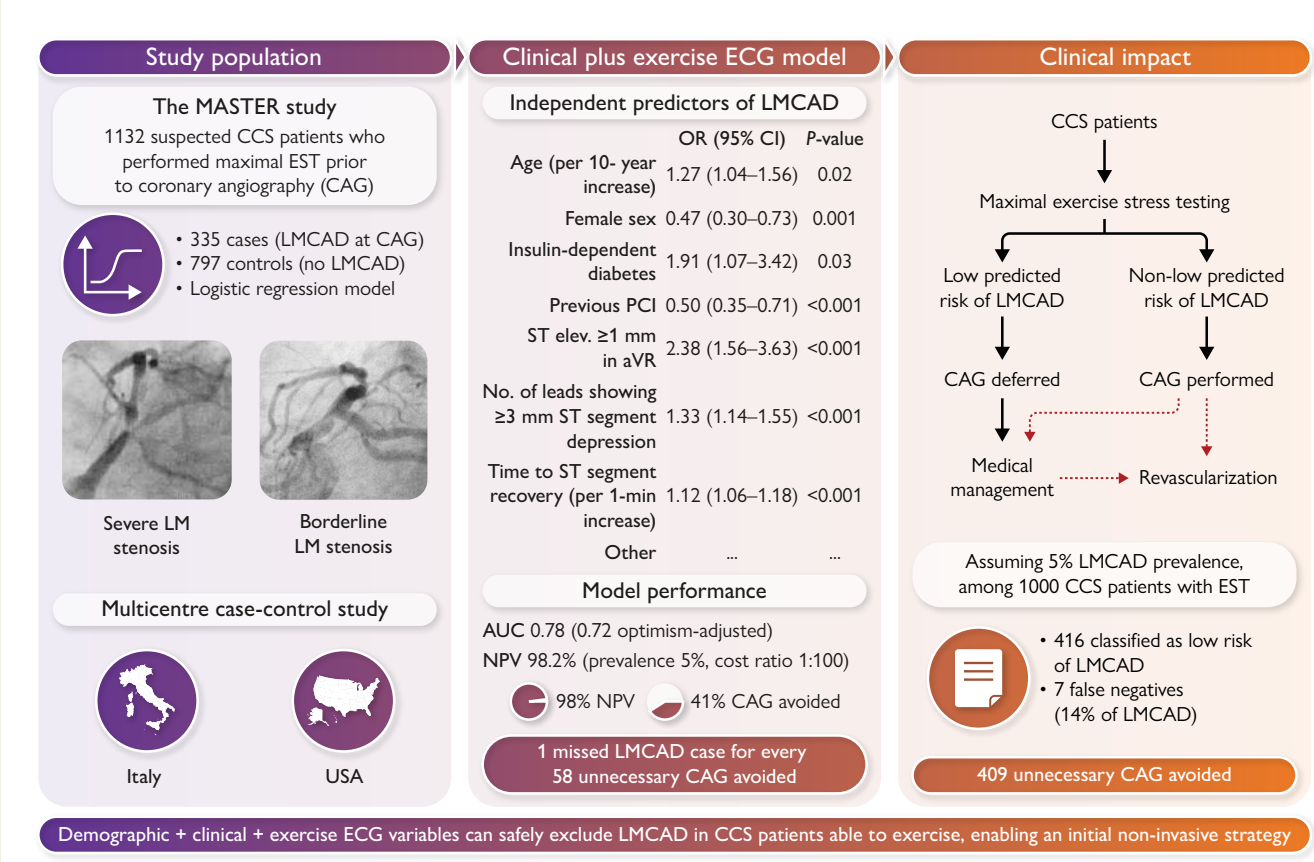
Can a model based only on clinical and exercise stress testing variables safely exclude obstructive left main or left main equivalent coronary artery disease (LMCAD) in patients with chronic coronary syndrome (CCS), reducing the need for routine invasive or CT coronary angiography?

Key Finding

In the MASTER study, a multicenter case-control study in patients with suspected CCS, a multivariable model achieved an optimism-adjusted area under the curve of 0.72 and a negative predictive value of 98% for the presence of left main or left main equivalent disease (LMCAD), allowing safe avoidance of coronary angiography in 41% of patients, missing 1 LMCAD per 58 unnecessary angiograms spared.

Take Home Message

This approach is potentially useful, particularly in communities where access to computed tomography coronary angiography is limited.



A prediction model based on clinical and exercise stress testing data (central table) has a 98.2% negative predictive value for the diagnosis of LMCAD on coronary angiography (CAG) in patients with chronic coronary syndromes (CCS). For a 5% prevalence of LMCAD among patients with suspected CCS undergoing a maximal exercise stress testing, the model allows to safely avoid CAG in 41% of the patients, while missing the diagnosis of LM disease in 0.7% of them

AUC, area under the curve; **CAG**, coronary angiography; **CCTA**, coronary computed tomography angiography; **CCS**, chronic coronary syndrome(s); **HR**, heart rate; **LMCAD**, left main coronary artery or left main equivalent disease; **NPV**, negative predictive value; **OR**, odds ratio

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Keywords Left main coronary artery disease • Left main stem • Left main equivalent • Exercise ECG stress test • Coronary computed tomography angiography • Myocardial ischaemia

Introduction

It is widely believed that the diagnosis of an angiographically significant (i.e. ≥50%) left main (LM) coronary artery stenosis is associated with the worst prognosis in coronary artery disease (CAD), for which current guidelines recommend revascularization even in clinically stable or asymptomatic patients with chronic coronary syndromes [CCS,[1,2] now the subject of a proposed nomenclature change using the more comprehensive term of 'non-acute myocardial ischemic syndromes' (NAMIS)[3]].

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial compared an initial non-invasive strategy of optimal medical therapy with or without revascularization using percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery in CCS patients and found no significant between-group differences during a median 3.2-year follow-up.[4] The study, by design, excluded patients with LMCAD through mandatory coronary computed tomography angiography (CCTA).[5] However, a more easily available, non-invasive diagnostic method, less expensive than CCTA to reliably exclude LMCAD, would allow a safer and more sustainable conservative treatment approach for the vast majority of CCS patients with suspected LMCAD. The ECG exercise stress test (EST) could be such a potential option, though its accuracy in diagnosing LMCAD has been variably reported.[6–9]

We designed the MAin stem Stenosis prediction Through Exercise Response (MASTER) study as a multicentre case-control study aimed at developing a simple and cost-effective non-invasive diagnostic model for excluding LMCAD and the so-called LMCAD-equivalent anatomy, still highly feared among cardiologists,[10,11] among patients referred to coronary angiography (CAG) for documented or suspected non-acute myocardial ischaemia and for whom a maximal EST was available.

Methods

The MASTER study is a retrospective multicentre case-control study. Patients were retrospectively identified among patients with suspected CCS who underwent CAG and performed an interpretable EST before CAG in 6 Italian (Pisa, Massa, Rome, Novara, Messina, Naples) and one US (the Mayo Clinic, Rochester, MN) hospitals between 2010 and 2024.

Participating investigators first identified, from their own CAG registries, patients with an angiographic stenosis ≥ 50% of the LM (LMCAD) or a stenosis ≥ 70% of both the proximal left anterior descending artery and the proximal circumflex artery (LMCAD-equivalent anatomy).[12] Such patients were then further screened if having 'suspected CCS', defined as the presence of any of the following conditions: (i) typical angina; (ii) atypical angina associated with more than two major risk factors for CAD (family history of premature CAD, cigarette smoking, diabetes, dyslipidaemia, peripheral artery disease); and (iii) inconclusive stress imaging test (i.e. single-photon emission computed tomography or stress echocardiography), irrespective of the presence and type of chest pain. Patients were excluded if they had suspected acute coronary syndrome (ACS), had previously undergone CABG surgery, or had a history of ACS and/or PCI in the previous 12 months. Patients were then further screened if they had had a maximal EST in the previous 2 months (achieving ≥80% of their maximum age-related heart rate during EST or with a test interrupted because of signs or symptoms of myocardial ischaemia) and excluded if they could not perform such a maximal EST or had an uninterpretable resting ECG (i.e. left bundle branch block, ventricular pacing, pre-excitation, or baseline ST-segment depression ≥1 mm). The decision to hold anti-anginal medications prior to the test was at the discretion of the ordering physicians, thus also reflecting the variable real-world current practice of withholding therapies before the EST. Thus, cases were identified as those patients with LMCAD or LMCAD-equivalent anatomy at CAG having an interpretable maximal EST. Although the ISCHEMIA trial did not exclude LMCAD-equivalent anatomies, we opted to group them with LMCAD because of their negative prognosis,[11] usually also prompting rapid revascularization.[10,13] We then identified controls by looking for three subjects who had undergone CAG for suspected CCS within 7 days of each case, also screened with the same criteria (suspected CCS and having had an interpretable maximal EST within 2 months of CAG, but not featuring LMCAD or LMCAD-equivalent). Thus, controls included patients with coronary anatomy varying from the total absence of CAD to three-vessel CAD but not fulfilling the definition of LMCAD and of LMCAD-equivalent anatomy. Our purpose, in fact, was to exclude the presence of LMCAD, not of severe CAD or multivessel CAD, as only patients with LMCAD, here subjected to a specific analysis, were excluded by design from the ISCHEMIA trial. The criteria for patient selection are detailed in *Figure 1*.

Patients with LMCAD stenosis ≥ 80% and patients with LMCAD-equivalent stenosis ≥ 80% were classified as severe LMCAD cases.

Demographic variables, baseline clinical and laboratory data, and data on medical therapy from medical records were collected. Exercise stress test–related variables were assessed by revision of the original tracings by experienced cardiologists (two at each participating centre) who had convened and preliminarily agreed on a uniform EST tracing interpretation and a comprehensive reporting method.[14,15] An electronic case report form with mandatory completion of all EST parameters was used for data collection. If an EST was not fully interpretable, the patient was excluded.

Evaluation of coronary angiography

Original CAGs were all re-analysed by means of a quantitative coronary angiography (QCA) software by two experienced investigators per centre. Quantitative coronary angiography was performed with the software available at each centre among the following: Axiom (Siemens Healthcare, Munich, Germany); SyncVision (Philips Healthcare, Best, the Netherlands); and Advantage Workstation (AW) Volume Share (General Electric Medical Systems, Milwaukee, WI, USA). The core lab in Pisa used the last. To ensure uniformity of the angiographic evaluations, a quality control was performed on the first 15 cases enrolled at each centre by the angiographic core lab at Pisa University Hospital, with an assessed inter-observer agreement of >96% on the degree of coronary stenosis as assessed by individual QCA evaluations. The high rate of inter-observer agreement at all centres permitted the avoidance of a core lab assessment of all CAGs.

Statistical methods

Continuous variables were summarized with medians and interquartile ranges (IQRs) and categorical variables with counts and percentages; such variables were compared using the Mann–Whitney test and the Fisher exact test, respectively.

Missing values represented <2% of the original data and were replaced by single imputation using predictive mean matching for numerical variables, logistic regression for binary variables, and polytomous regression for categorical variables with more than two levels.[16] For both outcomes, and for both cases and severe

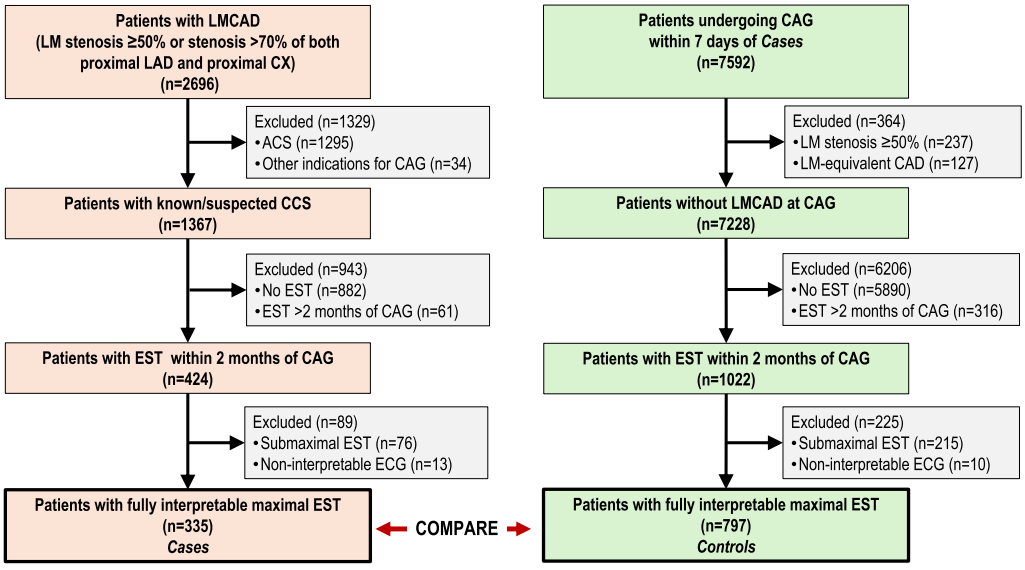

Figure 1 Patient disposition in the MASTER case-control study. ACS, acute coronary syndrome; CAD, coronary artery disease; CAG, coronary angiography; CCS, chronic coronary syndrome, CX, circumflex coronary artery; ECG, electrocardiogram; EST, exercise stress test; LAD, left anterior descending coronary artery; LM left main

cases, logistic regression models were fitted and odds ratios (ORs) were estimated. The initial set of variables included 26 clinical variables and 26 EST variables. Backward variable selection based on the Akaike Information Criterion (AIC) was applied to identify the best models. The performance of the selected models was quantified with the area under the curve (AUC) and the generalized Nagelkerke's R^2 index.

In the perspective of using the logistic model as a diagnostic tool, thresholds of the linear predictor to classify patients as cases or controls were chosen as the values minimizing the expected loss in classifying patients. The expected loss was based on the prevalence of cases in the reference population and the misclassification ratio (ratio between the cost of misclassifying a control, performing CAG in a subject without LMCAD, and the cost of misclassifying a case, not performing CAG in a patient with LMCAD). The prevalence of LMCAD among patients undergoing CAG for suspected CAD was assumed equal to 5%,[17–19] and misclassification ratios were assumed as 1:100 and 1:50.[20] For each threshold, the diagnostic accuracy of the model was quantified as optimism-adjusted sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). An internal validation of the risk prediction model was performed. First, a single imputation was applied to the original dataset. Then, 500 bootstrap samples were generated. For each sample, optimism was estimated by fitting an AIC-based model and selecting the optimal threshold. Finally, the average optimism across all bootstrap samples was calculated and used to correct the accuracy indexes.[21]

Model calibration was evaluated graphically for both the internal validation and the external validation on the Mayo Clinic subsample. As sensitivity analyses, and always with two (1:100 and 1:50) misclassification cost ratios, the following were performed:

(1) The model was developed using the data from the Italian centres and externally validated on the data from the US centre, assuming prevalences of LMCAD of 5% and .9%.
(2) The model was developed using the data received before August 2024 (n = 751, including 219 cases) and validated on the data received afterwards (n = 381, including 116 cases), assuming prevalences of LMCAD of 5% and .9%.
(3) The global model was developed also assuming a prevalences of LMCAD of .9%.

Finally, a sensitivity analysis was performed to compare the performance of the model when discriminating between controls and pure LMCAD cases (treating LM equivalents as controls), with the corresponding AUCs estimated along with their 95% confidence interval (CI).

Model calibration was evaluated graphically for both the internal validation and the external validation on the Mayo Clinic subsample.

Funding and role of the funding source

This study had no direct funding in any of its phases or sections. Indirect support was provided by institutional fundings at each participating centre. Participation was on a pure voluntary basis. Being it a retrospective and fully anonymized study, approval by Ethics Committees was not required.

Results

Study population

The study sample included 335 cases and 797 controls. Among cases, 101 had a LMCAD-equivalent coronary anatomy and 146 were classified as severe cases. Demographic and clinical characteristics of enrolled patients are reported in *Table 1* and Supplementary data online, *Table S1*. The median age of participants was 68 years (IQR, 61–74 years); 79% were men. Cases were slightly but significantly older than controls (median age 70 vs 68 years, $P < .001$) and included a higher proportion of men (86% vs 76%, $P < .001$). Additionally, cases had a significantly lower glomerular filtration rate, a higher proportion of diabetes, and a higher proportion of ranolazine users. They

Table 1 Demographic and clinical characteristics of the patients recruited according to the presence or absence of left main coronary artery disease or severe left main coronary artery disease

Variables	LMCAD			Severe LMCAD		
	No *n* = 797 (70%)	Yes *n* = 335 (30%)	*P*-value	No *n* = 986 (87%)	Yes *n* = 146 (13%)	*P*-value
Age, years	68 (61, 74)	70 (62, 76)	<.001	68 (61, 74)	70 (64, 76)	.002
Sex			<.001			.03
Male	602 (76)	289 (86)		766 (78)	125 (86)	
Female	195 (24)	46 (14)		125 (86)	21 (14)	
Weight, kg	78 (70, 87)	79 (70, 86)	.56	78 (70, 86)	79 (70, 88)	.26
Height, cm	170 (164, 177)	170 (165, 177)	.25	170 (165, 176)	172 (165, 178)	.17
BSA, m^2	1.9 (1.8, 2.1)	1.9 (1.8, 2.1)	.48	1.9 (1.8, 2.1)	1.9 (1.8, 2.1)	.2
BMI, kg/m^2	26.7 (24.5, 29.3)	26.4 (24.7, 29.4)	0,81	26.6 (24.4, 29.4)	26.4 (25.1, 29.1)	.47
LDL-C, mg/dL	87 (67, 114)	86 (63, 114)	.71	87 (65, 114)	87 (67, 116)	.36
HDL-C, mg/dL	44 (37, 53)	44 (36, 54)	.41	44 (37, 53)	44 (37, 54)	.99
Triglycerides, mg/dL	107 (77, 148)	106 (80, 138)	.84	106 (78, 145)	109 (82, 137)	.62
GFR, mL/min/1.73 m^2	82 (68, 92)	77 (64, 90)	.001	82 (68, 92)	73 (62, 88)	<.001
Smoking			.49			.63
Never	391 (49)	154 (46)		474 (48)	71 (49)	
Past	291 (37)	135 (40)		368 (37)	58 (40)	
Current	115 (14)	46 (14)		144 (15)	17 (12)	
Hypercholesterolaemia			.22			.37
No	390 (49)	150 (45)		476 (48)	64 (44)	
Yes	405 (51)	184 (55)		508 (52)	81 (56)	
Diabetes			.04			.75
No	566 (71)	225 (67)		691 (70)	100 (68)	
Yes, but not on insulin	194 (24)	82 (24)		240 (24)	36 (25)	
Yes, on insulin	36 (5)	28 (8)		54 (5)	10 (7)	
Hypertension			1,00			0,40
No	180 (23)	75 (22)		218 (22)	37 (25)	
Yes	616 (77)	260 (78)		767 (78)	109 (75)	
Serum uric acid > 6 mg/dL			.77			.76
Low	514 (70)	211 (69)		638 (70)	87 (69)	
High	220 (30)	95 (31)		275 (30)	40 (31)	
Family history of premature CVD			.008			.47
No	459 (58)	222 (66)		589 (60)	92 (63)	
Yes	337 (42)	113 (34)		396 (40)	54 (37)	
Previous PCI			.007			.03
No	565 (71)	264 (79)		711 (72)	118 (81)	
Yes	232 (29)	71 (21)		275 (28)	28 (19)	
Previous CAD			.21			.16
No CAD	482 (69)	218 (75)		605 (70)	95 (77)	

Continued

Table 1 ***Continued***

Variables	LMCAD			Severe LMCAD		
	No *n* = 797 (70%)	Yes *n* = 335 (30%)	*P*-value	No *n* = 986 (87%)	Yes *n* = 146 (13%)	*P*-value
CAD, but no previous MI	90 (13)	28 (10)		105 (12)	13 (11)	
Previous NSTEMI	61 (9)	23 (8)		74 (9)	10 (8)	
Previous STEMI	69 (10)	21 (7)		85 (10)	5 (4)	
Use of beta-blockers			.90			.79
No	369 (46)	153 (46)		453 (46)	69 (48)	
Yes	426 (54)	180 (54)		530 (54)	76 (52)	
Use of ACE-i			0,30			.85
No	530 (67)	211 (63)		645 (66)	96 (67)	
Yes	265 (33)	122 (37)		339 (34)	48 (33)	
Use of ARB			.07			.55
No	562 (71)	254 (76)		708 (72)	108 (74)	
Yes	233 (29)	80 (24)		276 (28)	37 (26)	
Use of CCB			.06			.06
No	617 (78)	241 (72)		757 (77)	101 (70)	
Yes	178 (22)	93 (28)		227 (23)	44 (30)	
Use of ranolazine			.002			.001
No	764 (96)	305 (91)		939 (95)	130 (90)	
Yes	31 (4)	29 (9)		45 (5)	15 (10)	
Use of nitrates			.34			.14
No	736 (93)	303 (91)		910 (92)	129 (89)	
Yes	59 (7)	31 (9)		74 (8)	16 (11)	
Use of anticoagulants			.05			.61
No	727 (91)	317 (95)		908 (92)	136 (94)	
Yes	68 (9)	17 (5)		76 (8)	9 (6)	
Use of aspirin			.53			.29
No	254 (32)	100 (30)		303 (31)	51 (35)	
Yes	541 (68)	234 (70)		681 (69)	94 (65)	
Use of DAPT			.93			1.00
No	678 (85)	286 (86)		840 (85)	124 (86)	
Yes	117 (15)	48 (14)		144 (15)	21 (14)	

Values are reported as *n* (%) or median (interquartile range). Missing per variable: weight *n* = 31; height *n* = 31; BSA *n* = 31; BMI *n* = 31; LDL-C *n* = 103; HDL-C *n* = 103; triglycerides *n* = 61; GFR *n* = 15; hypercholesterolaemia *n* = 3; diabetes *n* = 1; hypertension *n* = 1; serum uric acid *n* = 92; family history of premature cardiovascular disease *n* = 1; previous coronary artery disease *n* = 140; use of beta-blockers *n* = 4; use of ACE-i *n* = 4; use of ARB *n* = 3; use of CCB *n* = 3; use of ranolazine *n* = 3; use of nitrates *n* = 3; use of anticoagulants *n* = 3; use of aspirin *n* = 3; DAPT *n* = 3.
ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; CCB, calcium channel blocker; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; FTGM, Fondazione Toscana Gabriele Monasterio; GFR, glomerular filtration rate; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol: LMCAD, left main coronary artery disease; PCI, percutaneous coronary intervention.

also had a lower proportion of previous PCI and a lower proportion of family history of premature cardiovascular disease. The prevalence of severe left ventricular dysfunction [left ventricular ejection fraction (LVEF) ≤ 40%] was 5.8%.

Based on a *post hoc* inquiry with the participating centres, 95% of patients on beta-blockers (typically for 24–48 h) and of nitrates (for ≥24 h) had withdrawn these drugs before EST. No other medications were interrupted or reduced before the

performance of the EST. *Table 2* and Supplementary data online, *Table S2* summarize the EST parameters. Compared with controls, cases presented a significantly higher proportion of ST-segment depression in leads V2-V6, DI, DII, and DIII and of ST-segment elevation in aVR. They also had a higher proportion of angina, superimposed or counterclockwise ST-segment/heart rate loops, and longer ST-segment recovery time.

Prediction of left main coronary artery disease

Table 3 shows the ORs for LMCAD and severe LMCAD from the selected logistic regression models. Among demographic and clinical variables, significant predictors of LMCAD and severe LMCAD were older age, male sex, having lower values of glomerular filtration rate, absence of a previous PCI, and higher use of ranolazine. Among EST variables, significant predictors of LMCAD and severe LMCAD were a high baseline heart rate, a lower per cent of maximum theoretical heart rate, ST-segment elevation ≥ 1 mm in aVR, a longer time to ST-segment recovery, a higher number of leads showing 1.0–1.9 mm ST-segment depression, a higher number of leads showing 2.0–2.9 mm ST-segment depression, and a higher number of leads showing ≥3.0 mm ST-segment depression (these last three characteristics only for prediction of LMCAD).

The distributions of linear predictors of the diagnostic models are presented in *Figure 2A and C*. The AUC of the models were .78 (95% CI .75–.80) for the diagnosis of LMCAD and .82 (95% CI .79–.86) for the diagnosis of severe LMCAD (*Figure 2B and D*); the AUC adjusted for optimism were .72 and .75, respectively. The generalized R^2 was .27 for both the diagnosis of LMCAD and severe LMCAD, while optimism-adjusted values were .22 and .21, respectively.

Calibration curves of the models for cases and severe cases on internal validation are shown in Supplementary data online, *Figure S1*. For cases, the calibration curve corrected for optimism indicated good agreement between predicted and observed probabilities. For severe cases, the calibration curve showed some deviation from the ideal line for probabilities higher than .5, with wide CIs, reflecting the small number of cases. Calibration curves for the models predicting cases and severe cases, based on external validation using the Mayo Clinic sample, are presented in Supplementary data online, *Figure S2*. For cases, the 95% CI of the calibration curve includes the ideal line. In contrast, for severe cases, the calibration curve shows a notable deviation from the ideal line at predicted probabilities above .5. This and the wide CIs most likely reflect the limited number of severe cases in the Mayo Clinic validation dataset.

Optimism-adjusted performances of the models for the prediction of LMCAD and severe LMCAD are shown in *Table 4*. Estimates are provided at a prevalence of 5% for two different misclassification cost ratios:

(1) Assuming a misclassification cost ratio of 1:100, the model-predicted NPV was 98.2%. Among 1000 patients, 584 would be thus classified as cases (requiring CAG or CCTA to confirm diagnosis) and 416 as controls. Among predicted controls, 409 patients would be true negatives and 7 false negatives, thus saving 58 unnecessary CAGs for each LMCAD missed diagnosis (*Structured Graphical Abstract*).

Table 2 Stress electrocardiogram variables of the patients recruited according to the presence or absence of left main coronary artery disease or severe left main coronary artery disease

Variables	LMCAD			Severe LMCAD		
	No *n* = 797 (70%)	Yes *n* = 335 (30%)	*P*-value	No *n* = 986 (87%)	Yes *n* = 146 (13%)	*P*-value
Baseline HR, b.p.m.	73 (65, 83)	73 (64, 83)	.64	73 (65, 83)	74 (64, 85)	.63
Baseline systolic blood pressure, mmHg	130 (120, 146)	135 (120, 150)	.52	135 (120, 150)	130 (120, 148)	.78
Baseline diastolic blood pressure, mmHg	80 (75, 85)	80 (70, 85)	.09	80 (74, 85)	80 (70, 85)	.36
Peak METs	7.0 (5.9, 9.6)	7.0 (5.1, 8.7)	.04	7.0 (5.8, 9.9)	6.3 (5.1, 7.6)	<.001
Exercise duration, min	7.1 (5.5, 9.2)	7.0 (5.0, 9.4)	.15	7.0 (5.5, 9.2)	7.0 (5.0, 10.0)	.69
% of maximum theoretical HR	100 (94, 108)	99 (90, 109)	.05	101 (94, 109)	98 (89 108)	.01
HR at 1 min after stopping the exercise, b.p.m.	112 (100, 125)	110 (95, 121)	.01	112 (99, 124)	107 (94, 120)	.006
No. of leads showing 1.0–1.9 mm ST-segment depression	0 (0, 3)	2 (0, 3)	<.001	0 (0, 3)	2 (0, 3)	<.001
No. of leads showing 2.0–2.9 mm ST-segment depression	0 (0, 0)	0 (0, 2)	<.001	0 (0, 0)	0 (0, 2)	<.001
No. of leads showing ≥3.0 mm ST-segment depression	0 (0, 0)	0 (0, 0)	<.001	0 (0, 0)	0 (0, 0)	<.001

Continued

Table 2 *Continued*

Variables	LMCAD			Severe LMCAD		
	No *n* = 797 (70%)	Yes *n* = 335 (30%)	*P*-value	No *n* = 986 (87%)	Yes *n* = 146 (13%)	*P*-value
Time to ST-segment recovery, min	2 (0, 5)	5 (2, 7)	<.001	2 (0, 5)	5 (2, 8)	<.001
Angina			.003			.007
No	606 (76)	220 (67)		738 (75)	88 (62)	
Atypical	70 (9)	47 (14)		96 (10)	21 (15)	
Typical	119 (15)	62 (19)		149 (15)	32 (23)	
Dyspnoea			0,90			.72
No	741 (93)	306 (93)		914 (93)	133 (94)	
Yes	53 (7)	23 (7)		68 (7)	8 (6)	
ST-segment depression V2 ≥ 1 mm			<.001			.01
No	749 (94)	293 (87)		916 (93)	126 (86)	
Yes	48 (6)	42 (13)		70 (7)	20 (14)	
ST-segment depression V3 ≥ 1 mm			<.001			.002
No	658 (83)	230 (69)		789 (80)	99 (68)	
Yes	139 (17)	105 (31)		197 (20)	47 (32)	
ST-segment depression V4 ≥ 1 mm			<.001			<.001
No	465 (58)	120 (36)		540 (55)	45 (31)	
Yes	332 (42)	214 (64)		446 (45)	100 (69)	
ST-segment depression V5 ≥ 1 mm			<.001			<.001
No	386 (48)	79 (24)		439 (45)	26 (18)	
Yes	411 (52)	256 (76)		547 (55)	120 (82)	
ST-segment depression V6 ≥ 1 mm			<.001			<.001
No	398 (50)	83 (25)		454 (46)	27 (19)	
Yes	399 (50)	251 (75)		532 (54)	118 (81)	
ST-segment elevation ≥ 1 mm in aVR			<.001			<.001
No	730 (92)	241 (73)		875 (89)	96 (66)	
Yes	64 (8)	91 (27)		106 (11)	49 (34)	

Continued

Table 2 *Continued*

Variables	LMCAD			Severe LMCAD		
	No *n* = 797 (70%)	Yes *n* = 335 (30%)	*P*-value	No *n* = 986 (87%)	Yes *n* = 146 (13%)	*P*-value
ST-segment depression DI ≥ 1 mm			<.001			.04
No	737 (93)	285 (86)		900 (91)	122 (86)	
Yes	58 (7)	46 (14)		84 (9)	20 (14)	
ST-segment depression DII ≥ 1 mm			<.001			<.001
No	675 (85)	220 (66)		810 (82)	85 (59)	
Yes	122 (15)	112 (34)		176 (18)	58 (41)	
ST-segment depression DIII ≥ 1 mm			<.001			<.001
No	702 (88)	250 (75)		850 (86)	102 (71)	
Yes	95 (12)	82 (25)		136 (14)	41 (29)	
ST/HR loop			<.001			<.001
Clockwise	490 (70)	181 (57)		601 (69)	70 (49)	
Superimposed or counterclockwise	214 (30)	135 (43)		275 (31)	74 (51)	
Ventricular premature beats before beginning of exercise			.91			.53
Absent	729 (92)	305 (91)		899 (91)	135 (93)	
≥1 in a 30 s strip	67 8)	29 (9)		86 (9)	10 (7)	
Ventricular premature beats after beginning of exercise			.05			.58
Absent	471 (59)	218 (65)		604 (61)	85 (59)	
≥1 in a 30 s strip	326 (41)	116 (35)		382 (39)	60 (41)	
Ventricular tachycardia during exercise			.14			.42
No	749 (94)	322 (96)		931 (95)	140 (97)	
Yes	47 (6)	12 (4)		54 (5)	5 (3)	

Values are reported as *n* (%) or median (interquartile range). Missing per variable: baseline HR *n* = 22; baseline systolic blood pressure *n* = 30; baseline diastolic blood pressure *n* = 30; peak METs *n* = 176; HR 1 min after stopping the exercise *n* = 59; exercise duration *n* = 26; no. of leads showing ST-segment depression ≥ 2 *n* = 4; no. of leads showing ST-segment depression ≥ 3 mm *n* = 3; no. of leads showing ≥1 mm ST-segment depression *n* = 6; angina *n* = 8; dyspnoea *n* = 9; ST-segment depression DI ≥ 1 mm *n* = 6; ST-segment depression DII ≥ 1 mm *n* = 3; ST-segment depression DIII ≥ 1 mm *n* = 3; ST-segment depression V4 ≥ 1 mm *n* = 1; ST-segment depression V6 ≥ 1 mm *n* = 1; ST/HR loop *n* = 112; time to ST-segment recovery *n* = 84; ventricular premature beats before beginning of exercise *n* = 2; ventricular premature beats after beginning of exercise *n* = 1; ventricular tachycardia during exercise *n* = 2.
HR, heart rate; LMCAD, left main coronary artery disease; MET, metabolic equivalent.

Table 3 Odds ratio and 95% confidence intervals from the logistic model for any left main coronary artery disease and the logistic model for severe left main coronary artery disease

	LMCAD		Severe LMCAD	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Clinical variables				
Age, 10-year increase	1.27 (1.04–1.56)	.02	1.43 (1.10–1.87)	.009
Sex (female vs male)	.47 (.30–.73)	.001	.57 (.34–.98)	.04
Weight, 1 kg increase	.84 (.66–1.05)	.12		
Height, 1 cm increase	.92 (.82–1.03)	.13		
Body surface area, 1 cm^2 increase	1.16 (.96–1.41)	.12		
LDL cholesterol, 10 mg/dL increase			1.05 (1.00–1.11)	.07
Triglycerides, 10 mg/dL increase	.98 (.95–1.00)	.11		
Glomerular filtration rate, 10 mL/min/1.73 m^2 increase	.91 (.83–.99)	.03	.89 (.79–1.00)	.05
Diabetes		.07		
Yes, but not on insulin vs no	.92 (.65–1.30)			
Yes, on insulin vs no	1.91 (1.07–3.42)			
Previous percutaneous coronary intervention				
Yes vs no	.50 (.35–.71)	<.001	.22 (.07–.68)	.01
Previous CAD				.10
Previous CAD vs no CAD			3.41 (1.02–11.42)	
Previous NSTEMI vs no CAD			3.21 (1.01–10.23)	
Previous STEMI vs no CAD			1.39 (.35–5.52)	
Use of ranolazine				
Yes vs no	2.53 (1.37–4.68)	.003	2.61 (1.27–5.36)	0,01
Use of anticoagulants				
Yes vs no	.59 (.31–1.11)	0,10		
ECG variables				
Baseline heart rate, 10 b.p.m. increase	1.19 (1.06–1.33)	.003	1.32 (1.14–1.53)	<.001
Baseline systolic blood pressure, 10 mmHg increase			.90 (.81–1.00)	.07
Baseline diastolic blood pressure, 10 mmHg increase	.87 (.75–1.02)	.09		
% of maximum theoretical heart rate, 10 unit increase	.84 (.71–.99)	.04	.75 (.60–.95)	.01
Heart rate at 1 min after stopping the exercise, 10 b.p.m. increase	.91 (.81–1.01)	.08	.84 (.72–.97)	**.02**
Dyspnoea				
Yes vs no			.49 (.20–1.24)	.13
ST-segment depression V6 ≥ 1 mm				
Yes vs no			1.76 (1.00–3.10)	.05
ST-segment elevation ≥ 1 mm in aVR				
Yes vs no	2.38 (1.56–3.63)	<.001	2.10 (1.24–3.56)	.006
No. of leads showing 1.0–1.9 mm ST-segment depression	1.13 (1.02–1.24)	.02		
No. of leads showing 2.0–2.9 mm ST-segment depression	1.14 (1.03–1.27)	.01		
No. of leads showing ≥3.0 mm ST-segment depression	1.33 (1.14–1.55)	<.001		
ST-segment depression DII ≥ 1 mm				

Continued

Table 3 *Continued*

	LMCAD		Severe LMCAD	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Yes vs no			1.86 (1.14–3.06)	.01
ST/HR loop				
Superimposed or counterclockwise vs clockwise	1.36 (.98–1.89)	.06	1.58 (1.03–2.42)	.04
Time to ST-segment recovery, min	1.12 (1.06–1.18)	<.001	1.13 (1.06–1.21)	<.001
Ventricular premature beats after beginning of exercise				
Yes vs no	.79 (.58–1.07)	.12		

ORs and 95% CIs from the logistic model for any LMCAD and the logistic model for severe LMCAD. Empty cells refer to variables not included in the corresponding model.
CI, confidence interval; HR, heart rate; LDL, low-density lipoprotein; LMCAD, left main coronary artery disease; NSTEMI, non-ST-elevation myocardial infarction; OR, odds ratio; STEMI, ST-elevation myocardial infarction.

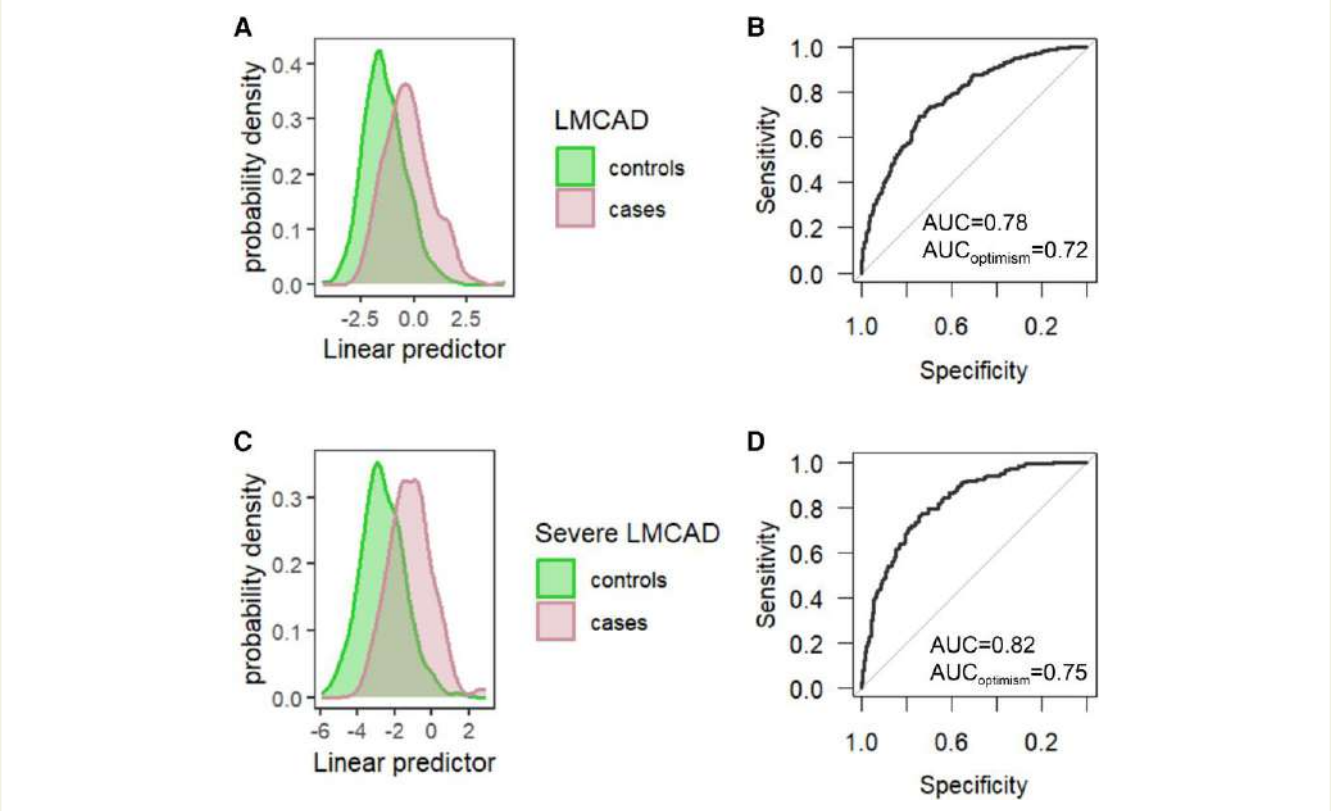

Figure 2 Distributions of the linear predictors from the logistic regression models and corresponding receiver-operating characteristic curves. (*A*) Distributions of the linear predictor from the logistic regression model for left main (LM) stenosis ≥ 50% (*A*), with the corresponding receiver-operating characteristic curve (*B*). Distributions of the linear predictor from the logistic regression model for LM stenosis ≥ 70% (*C*), with the corresponding receiver-operating characteristic curve (*D*)

Under the same conditions, considering severe LMCAD, the model-predicted NPV was 98.5%. Among 1000 patients, 565 would be thus classified as cases (requiring CAG or CCTA to confirm diagnosis) and 435 as controls. Among predicted controls, 429 patients would be true negatives and 6 false negatives, thus saving 72 unnecessary CAGs for each severe LMCAD missed diagnosis.

(2) Assuming a misclassification cost ratio of 1:50, the models were slightly less accurate, with NPV of 97.7% and 97.9% for LMCAD and severe LMCAD, respectively. This scenario

Table 4 Model accuracy measures, with adjustment for optimism, and expected false negatives and true positives assuming a 5% prevalence of left main coronary artery disease and a misclassification cost ratio of 1:100 and 1:50

	Misclassification cost ratio	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	True positives (%)	False positives (%)	True negatives (%)	False negatives (%)	False negatives: true negatives
LMCAD	1:100	85.3	43.0	7.3	98.2	4.3	54.1	40.9	.7	1:58
	1:50	74.4	56.7	8.3	97.7	3.7	41.1	53.9	1.3	1:41
Severe LMCAD	1.100	87.2	45.1	7.7	98.5	4.4	52.1	42.9	.6	1:72
	1:50	74.9	61.7	9.3	97.9	3.7	36.3	58.7	1.3	1:45

LMCAD, left main coronary artery disease.

would result in saving 41 unnecessary CAGs for each LMCAD missed diagnosis and 45 unnecessary CAGs for each severe LMCAD missed diagnosis.

In the first sensitivity analysis, the validation on the Mayo Clinic sample of the models developed from the Italian data provided AUCs of .73 (95% CI .62–.83) and .76 (95% CI .63–.88), respectively, similar to the values adjusted for optimism. The NPVs and the sensitivity on the Mayo Clinic sample did not materially change compared with the optimism-adjusted measures of the main model and only slightly decreased for severe LMCAD (see Supplementary data online, *Table S3*). Similar results were obtained by assuming an LMCAD prevalence of .9% (see Supplementary data online, *Table S4*).

In the second sensitivity analysis, validation of the model according to the time of data accrual provided AUCs of .70 (95% CI .65–.76) and .69 (95% CI .62–.76), respectively. Also in this case, NPVs of the externally validated models for LMCAD did not materially change compared with the optimism-adjusted NPV of the main model and only slightly decreased for severe LMCAD prediction (see Supplementary data online, *Table S5*). Again, values were extremely similar in the analysis that assumed a prevalence of LMCAD of .9% (see Supplementary data online, *Table S6*).

In the third sensitivity analysis, the global model was recalibrated assuming a prevalence of LMCAD of .9%. Similar values for the NPV were again observed (see Supplementary data online, *Table S7*).

No material differences were finally observed in the model performance when discriminating between 'pure' LMCAD cases, and all other controls, this time including LMCAD-equivalents (see Supplementary data online, *Table S8*). No material differences were also observed in sensitivity analyses reporting the model performances for LMCAD and LMCAD-equivalents where one centre at a time was excluded from the training set and used as validation set (see Supplementary data online, *Figure S3*).

Discussion

This study shows that a combination of demographic, clinical, and EST variables can exclude, with high effectiveness, the presence of LMCAD in patients able to perform a maximal EST, with a NPV around 98% for cases and severe cases. For a misclassification cost ratio of 1:100 (1:50) and a prevalence of 5%, our model correctly classifies as LMCAD cases, requiring anatomical assessment through CAG or CCTA, 85% (74%) of true LMCAD cases. This translates into the cost of missing the LMCAD diagnosis in 7 (13) out of 1000 patients undergoing EST for suspected CAD, but allowing the safe avoidance of CAG or CCTA in 41% (54%) of all patients with suspected CCS performing a maximal, interpretable EST. The corresponding estimated ratios between the number of missed LMCAD diagnoses and that of unnecessary CAGs saved are 1:58 and 1:41 for the two above-detailed misclassification cost ratios. Comparable performances were obtained for severe cases.

Such results may have implications for the current clinical management of patients with CCS, allowing to avoid a large number of CAGs or CCTA otherwise required to exclude

LMCAD, especially in countries or communities where access to CCTA is financially or logistically restricted.

Evidence about optimal management of LMCAD in trials comparing revascularization with contemporary optimal medical therapy is lacking, and recommendations for revascularization in LMCAD are based on now obsolete studies, performed at times when optimal medical therapy was much poorer than nowadays and reporting a 37% 3-year survival rate without revascularization.[22] On the other hand, 5-year mortality in patients undergoing revascularization for LMCAD is still as high as 11% in recent randomized clinical trials.[23] Left main coronary artery disease patients were, therefore, excluded from randomized trials comparing revascularization with optimal medical therapy, such as COURAGE[24] and ISCHEMIA.[4] These trials showed that contemporary optimal medical therapy is a reasonable alternative to immediate revascularization in patients in whom LMCAD was excluded, as done with the routine use of CCTA in the more recent ISCHEMIA trial.[4] It has been argued that there is a contemporary need to challenge the traditional fear for optimal medical therapy alone in managing LMCAD or LMCAD-equivalents, especially in less severe cases.[25] Despite this, however, the main message of ISCHEMIA—similar major outcomes with revascularization plus optimal medical therapy or with optimal medical therapy alone—cannot be generalized to the entire population of CCS patients because of the lingering concern that some of these patients may harbour LMCAD. As a consequence, when CCTA is unavailable, CAG is generally performed to ascertain coronary anatomy, and this often triggers revascularization of all angiographically significant stenoses.[26] Ruling out LMCAD with a non-invasive and easily available test may therefore be a useful, not-to-be-superficially-dismissible tool, and mainly where CCTA is not routinely available, which is certainly the case all around Europe,[27] and even more in less-affluent parts of the world. In addition to the availability and to cost issues, CCTA has itself limitations: it is often non-diagnostic in cases of extreme body weight and extensive coronary calcifications, entails the risk of contrast-induced or worsened nephropathy, is prone to false positives in the presence of eccentric stenoses, and has a high but still not perfect (95%) NPV.[28,29]

Several attempts have been made in the past to diagnose LMCAD with EST. Findings suggestive of LMCAD include diffuse and severe ST-segment deviation, significant ventricular arrhythmias or hypotension during exercise, or the slow recovery of ST-segment depression after exercise cessation.[30] These are, however, strong elements to suspect extensive CAD, but not to specifically identify the presence of LMCAD. A recent report from the ISCHEMIA trial concluded that clinical and EST parameters were only weakly predictive of LMCAD on CCTA and that for most patients with moderate or severe ischaemia anatomical imaging is needed to rule out LMCAD.[31] That report was, however, limited by the lack of granular data on EST tracings and by the lack of a comprehensive ECG evaluation. Most recently, Godoy and co-workers evaluated the feasibility of predicting LMCAD by means of logistic regression and machine learning models in a cohort of 150 000 CCS patients undergoing elective CAG after stress testing.[19] All models resulted in only moderate discrimination. However, also this study lacked detailed information on cardiac stress tests (only aggregated risk information was available) and had a large number of missing laboratory tests.

The novelty of our work consists in building a model aimed at maximizing the NPV, i.e. minimizing the probability of missing LMCAD and severe LMCAD cases, and exploiting a number of EST variables, in a comprehensive evaluation, in addition to the usual ST-segment depression. The aim was here, therefore, not to improve the pre-CAG diagnosis of LMCAD, but to rule it out, to avoid unnecessary referral to CAG. Our model indeed allows avoiding CAD in a substantial 42%–55% of patients undergoing EST for suspected CCS. Based on findings from the ISCHEMIA trial, this would translate into halving the costs of hospitalization for CAG and without affecting the prognosis of patients not having LMCAD. As to the safety of adopting our approach avoiding the routine use of CAG, one may add that no contemporary evidence supports the absolute need of immediate revascularization in patients with LMCAD without signs and symptoms of acute ischaemia. In further addition, the threatened risk of sudden cardiac death in LMCAD patients not being revascularized is certainly diminished with contemporary optimal medical therapy: in ISCHEMIA, patients with three-vessel CAD, even with >70% proximal left anterior descending artery stenosis, featured an incidence of sudden death of 1.3% at 3.2 years of follow-up (annualized rate .4%/year). Importantly, there were no differences in sudden cardiac deaths between the invasive and the conservative strategy (hazard ratio .78, 95% CI .48–1.27).[32] Furthermore, initially missing the diagnosis of LMCAD in 14% of patients harbouring this condition does not preclude the possibility to diagnose LMCAD by performing CAG or CCTA if symptoms persist or worsen despite optimal medical therapy. Our model, therefore, offers a practical and efficient algorithm for screening CCS patients able to exercise in their referral to CAG.

The NPV of 98% of our model after adjusting for optimism is the highest reported so far for LMCAD prediction based on EST parameters. Highest values previously reported ranged from 94% to 97%.[33,34] Together with the high optimism-adjusted AUC, such value supports the adoption of our model in the diagnostic workflow of suspected CCS. We acknowledge that routine CCTA in patients with suspected CCS may represent a better option in the near future, assuming improved availability and affordability. Nonetheless, CCTA has only acceptable concordance with invasive CAG for the detection of LMCAD (intraclass correlation coefficient .63, sensitivity 85%, specificity 84%[35]), leaving ample room for missing LMCAD diagnosis even if performed. Invasive CAG is the only anatomical alternative to CCTA at the moment, but it would entail increased health costs for the hospitalization and the risk of unnecessary revascularizations in non-LMCAD cases, way too often triggered by the mere anatomical assessment.[26]

In the present study, we assumed the prevalence of LMCAD of 5% in the population of patients undergoing EST for suspected CCS. This estimate was chosen based on the largest reports in recent literature,[17–19] but we have also here performed a sensitivity analysis based on a prevalence of LMCAD of .9%. This lower prevalence might be expected in contemporary clinical practice, thanks to improvements in cardiovascular risk factor management. A lower prevalence of LMCAD would further increase sensitivity and NPV of our model, making its adoption even more advantageous in terms of health cost reduction.

Prospective validation of our algorithm in consecutive patients presenting with pre-test probability of obstructive CAD of >5% using the 2024 CCS guidelines[36] would enhance its generalizability. However, we believe that making our algorithm

easily available through an app for mobile devices, rapidly yielding an estimate of the likelihood of LMCAD or severe LMCAD for the practicing cardiologist, would improve decision-making in CCS cases. The aid of artificial intelligence is expected to further improve the NPV of an agile and affordable diagnostic tool, such as those incorporating EST-derived parameters.

Study limitations

We readily recognize several limitations of the approach here proposed to rule out the presence of LMCAD.

The first limitation is that these findings, based on a retrospective analysis, but of a very large number, of LMCAD cases, are only applicable to patients able to exercise and to perform a maximal and fully interpretable EST (79% of our exercising patients with an interpretable EST had a maximal test). In our study, the proportion of patients with left bundle branch block, ventricular pacing, pre-excitation, or ≥1 mm ST-depression at baseline was as low as 3%, but this is because ECG abnormalities at rest were a contraindication to the prescription of an EST (referral bias); thus, they were mostly an unexpected finding when performing EST. It is clear that our decision algorithm is not applicable in the presence of baseline ECG abnormalities precluding ECG interpretation during EST; however, the prevalence of left bundle branch block or ventricular pacing was rather low (5.5%) in the CLARIFY registry, enrolling 32 703 outpatients with stable CAD worldwide.[37] In our population, the prevalence of severely reduced LVEF ≤40% was very low (5.8%), in keeping with the findings of the CLARIFY registry.[37] Thus, our results do not necessarily apply to the population with severely depressed LVEF, mostly excluded from the EST.

A second, but only apparent, limitation is that we mainly used an internal validation. Recent literature has however discussed advantages and disadvantages of internal vs internal-external vs external validations of a clinical prediction model,[38] concluding for the preferability of our choice for the primary analysis here performed. To further validate it, however, we also performed an external validation against the US cohort here involved, as well as splitting the cohort according to the date of CAG, with nearly identical results.

A third limitation is the lack of routine intracoronary imaging for the evaluation of plaque burden features or physiological assessment of LMCAD, now increasingly but still not routinely performed. Finally, one may object that our model features an acceptable, but still imperfect sensitivity. The main point, however, is its very high NPV, allowing to avoid CAG in 42% of patients showing signs of myocardial ischaemia using a misclassification cost of 1:100. We indeed consider the balance of one missed LMCAD case vs 58 unnecessary CAGs avoided in non-LMCAD patients (*Structured Graphical Abstract*) as highly favourable, also considering that alternative methods are also imperfect in excluding LMCAD diagnosis.

Additionally, women were under-represented in our study population. This likely reflects real-world referral patterns for invasive evaluation rather than intentional selection. A prospective validation of our findings in more sex-balanced cohorts is warranted.

As a further limitation, one may dispute the choice of the misclassification ratios of 1:50 and 1:100, which to us, however, appears unbiased and most balanced.

Finally, our study was not designed to investigate the prognosis of patients with LMCAD; therefore, we cannot provide a prognostic validation of our diagnostic algorithm.

Conclusions

The combination of demographic, clinical, and ECG variables from the usually neglected EST can effectively direct patients with suspected CCS to an appropriate initial management with optimal medical therapy alone,[39] being able to reasonably exclude the presence of LMCAD, averting or deferring unnecessary CAG or CCTA. If implemented, this tool would streamline management and optimize costs in a discrete proportion of CCS cases and especially in communities where CCTA is not readily available.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

Nothing to declare related to this specific manuscript. Disclosure paragraph is appended in the main text. ICMJE forms were submitted separately. M.D.C. declares fees and honoraria from Boston Scientific, Medtronic, Merit, Microport, and Sanofi, all unrelated to the present manuscript. P.L.T. declares fees and honoraria from Daiichi Sankyo, Novo Nordisk, AstraZeneca, Novartis, and Servier, all unrelated to the present manuscript. L.Bag. has no conflict of interest to declare. L.Baz. has no conflict of interest to declare. S.B. has no conflict of interest to declare. P.C. declares honoraria from Sanofi, Amgen, and Novartis, all unrelated to the present manuscript. L.C. has no conflict of interest to declare. A.R.D.C. has no conflict of interest to declare. S.F. has no conflict of interest to declare. M.F. has no conflict of interest to declare. A.G. has no conflict of interest to declare. E.H. has no conflict of interest to declare. G.A.L. has no conflict of interest to declare. A.L. has no conflict of interest to declare. M.A.M. has no conflict of interest to declare. N.M. has no conflict of interest to declare. C.M. has no conflict of interest to declare. D.N. has no conflict of interest to declare. M.C.P. has no conflict of interest to declare. G.P. declares fees, honoraria, and research funding from Amgen, Sanofi, Novartis, Daiichi Sankyo, Amarin, Malesci, PIAM, Boehringer Ingelheim, Bayer, Pfizer/BMS, AstraZeneca, Biotronik, Medtronic, Abbott, Edwards, Novo Nordisk, Chiesi, Servier, Boston, Bruno Farmaceutici, and J&J, all unrelated to the present manuscript. S.T. has no conflict of

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Data Availability

Data from this analysis will be disclosed upon reasonable request.

Funding

Nothing to declare.

Ethical Approval

Ethical approval was not required.

Pre-registered Clinical Trial Number

Not applicable.

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