SUPPLEMENTAL MATERIAL

Risk scores and coronary artery disease in patients with suspected acute coronary syndrome and intermediate cardiac troponin concentrations

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Supplemental Text 1. Risk scores calculation

To our knowledge, each risk score was calculated using the most recent version reported in the literature [1-7]. An R function was created for each risk score to allow for row wise calculation of risk scores in all patients. The R package "RiskScoresevd" was developed for the reproducibility of this analysis using any adequate dataset (https://github.com/dvicencio/RiskScoresevd)[8]. After calculating each patient's risk score, risk classification was assigned based on the corresponding thresholds. According to the ACC guidelines 2023, a HEART score of ≤ 3 or EDACS <16 discharge without further testing is reasonable, provided access to rapid follow-up is available [9]. We therefore stratified the classifications to binary, either "lowest risk" (HEART ≤ 3 , EDACS <16 [further steps are recommended for EDACS, *Table A*], GRACE ≤ 88 , ASCVD <.05 or 5%, SCORE2 <5%, SCORE2-OP<7.5% [*Table B*]) or "above lowest risk". An exploration of the data was performed to ensure all variables required to calculate the risk scores were available or could be derived (*Figure 1 and Supplemental Figure 2*). When derivation was required, insight from two clinicians was given. Missing data values were imputed using MICE R package following the protocol suggested by Jakobsen et. al [10] (*Figure 2B*).

Table A. EDACS additional considerations to categorise patients.

Low risk cohort:	Not low risk cohort:
EDACS <16 and	EDACS ≥ 16 or
ECG shows no new ischaemia and	ECG shows new ischaemia or
0-hr and 2-hr troponin both negative.	0-hr or 2-hr troponin positive.

Table B. SCORE2/OP additional considerations to categorise patients in the UK based on age.

	Low risk	Moderate Risk	High risk
< 50 years	<2.5%	2.5 to <7.5%	≥7.5%
50 – 69 years	<5%	5 to <10%	≥10%
≥ 70 years	<7.5%	7.5 to <15%	≥15%

Variable	All participants, (n = 103)	No coronary artery disease, (n = 42)	Any coronary artery disease, (n = 61)	p-value ¹
Female	35 (34%)	17 (40%)	18 (30%)	0.25
Аде	61 (13)	55 (12)	65 (11)	<0.001
Presenting symptom	01 (10)		00 (11)	0.001
Chest Pain	84 (82%)	32 (76%)	52 (85%)	0.24
Anginal symptoms	42 (41%)	19 (45%)	23 (38%)	0.21
Cardiovascular risk factor	12 (1170)	19 (1370)	25 (5070)	0.11
BMI kg/m2	29.5 (5.9)	299(49)	29.2 (6.5)	0.33
Current or previous cigarrete smoker	52 (50%)	16 (38%)	36 (59%)	0.037
Hypertension	41 (40%)	10 (24%)	31 (51%)	0.006
Diabetes	12 (12%)	3 (7.1%)	9 (15%)	0.35
Hyperlipidemia	27 (26%)	10 (24%)	17 (28%)	0.70
Family history	33 (32%)	16 (38%)	17 (28%)	0.27
Chronic kidney disease	7 (6.8%)	2 (4.8%)	5 (8.2%)	0.70
Medical history				
Angina	0 (0%)	0 (0%)	0 (0%)	
Myocardial infarction	0 (0%)	0 (0%)	0 (0%)	
Stroke	5 (4.9%)	2 (4.8%)	3 (4.9%)	>0.99
Peripheral vascular disease	1 (1.0%)	0 (0%)	1 (1.6%)	>0.99
Physiology and investigations				
Myocardial ischemia on ECG	6 (5.8%)	1 (2.4%)	5 (8.2%)	0.40
T-wave inversion	11 (11%)	3 (7.5%)	8 (13%)	0.52
Heart rate, bmp	80 (18)	78 (20)	81 (16)	0.36
Systolic BP, mm Hg	153 (26)	153 (21)	152 (29)	0.42
Hemoglobin, g/L	143 (14)	143 (16)	143 (12)	0.73
Creatine	78 (16)	80 (19)	77 (14)	0.63
eGFR, mL/min/1.73 m2	85 (17)	87 (19)	84 (16)	0.43
Total cholesterol, mmol/L	5.17 (1.13)	5.29 (0.89)	5.09 (1.27)	0.30
LDL cholesterol, mmol/L	3.25 (1.05)	3.41 (0.90)	3.14 (1.13)	0.27
Peak troponin I concentration, ng/L	8 (6, 12)	8 (7, 13)	8 (6, 11)	0.63
Clinical risk scores				
HEART	4 (3, 4)	3 (2, 4)	4 (3, 5)	0.001
EDACS	14 (12, 20)	13 (9, 17)	17 (12, 21)	0.011
GRACE	72 (56, 89)	57 (44, 72)	85 (67, 100)	< 0.001

Supplemental Table 1. Baseline characteristics patients without known previous coronary artery disease stratified by findings on coronary computed tomography angiography.

Variable	All participants, (n = 103)	No coronary artery disease, (n = 42)	Any coronary artery disease, (n = 61)	p-value ¹
TIMI	1 (0, 1)	0 (0, 1)	1 (0, 1)	< 0.001
PCE	0.15 (0.07, 0.32)	0.08 (0.04, 0.16)	0.22 (0.11, 0.34)	< 0.001
SCORE2/OP	8 (5, 13)	5 (4, 9)	12 (6, 17)	< 0.001

Supplemental Table 1. Baseline characteristics patients without known previous coronary artery disease stratified by findings on coronary computed tomography angiography.

Values are median (interquartile range), n (%) or mean \pm SD. ¹ Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test. BMI = body mass index; BP = blood pressure; bmp = beats per minute; CABG = coronary artery bypass grafting; CAD = coronary artery disease; ECG = electrocardiogram; EDACS = Emergency Department Assessment of Chest Pain Score; eGFR = estimated glomerular filtration rate; GRACE 2.0 = Global Registry of Acute Coronary Events version 2.0; HEART = History, ECG, Age, Risk factors, Troponin; LDL = low-density lipoprotein; PCE = pooled cohort equations; PCI = percutaneous coronary intervention; SCORE2/OP = Systematic COronary Risk Evaluation 2/Older Population; TIMI = Thrombolysis In Myocardial Infarction.

Supplemental Table 2. Baseline characteristics of patients stratified by the presence or absence of obstructive coronary artery disease.

Variable	All participants, (n = 167)	No coronary artery disease, (n = 47)	Non- obstructive coronary artery disease, (n = 70)	Obstructive coronary artery disease, (n = 50)	p-value ¹
Female	46 (28%)	19 (40%)	18 (26%)	9 (18%)	0.044
Age	64 (12)	56 (13)	65 (11)	70 (10)	< 0.001
Presenting symptom					
Chest Pain	143 (86%)	37 (79%)	60 (86%)	46 (92%)	0.19
Anginal symptoms	76 (46%)	21 (45%)	32 (46%)	23 (46%)	>0.99
Cardiovascular risk factor					
BMI kg/m2	29.3 (5.8)	29.6 (5.2)	29.7 (6.3)	28.5 (5.6)	0.51
Current or previous cigarrete smoker	89 (53%)	18 (38%)	38 (54%)	33 (66%)	0.026
Hypertension	79 (47%)	11 (23%)	39 (56%)	29 (58%)	< 0.001
Diabetes	30 (18%)	3 (6.4%)	14 (20%)	13 (26%)	0.027
Hyperlipidaemia	33 (20%)	10 (22%)	17 (24%)	6 (12%)	0.22
Family history	64 (38%)	17 (36%)	29 (41%)	18 (36%)	0.83
Chronic kidney disease	19 (11%)	2 (4.3%)	8 (11%)	9 (18%)	0.10
Medical history					
Angina	34 (20%)	2 (4.3%)	14 (20%)	18 (36%)	< 0.001
Myocardial infarction	40 (24%)	3 (6.4%)	16 (23%)	21 (42%)	< 0.001
Stroke/TIA	13 (7.8%)	2 (4.3%)	6 (8.6%)	5 (10%)	0.58
Peripheral vascular disease	6 (3.6%)	0 (0%)	1 (1.4%)	5 (10%)	0.021
Previous revascularization					
PCI	40 (24%)	3 (6.4%)	15 (21%)	22 (44%)	< 0.001
CABG	10 (6.0%)	0 (0%)	7 (10%)	3 (6.0%)	0.071
Physiology and investigations					
Myocardial ischaemia on ECG	8 (4.8%)	3 (6.4%)	4 (5.7%)	1 (2.0%)	0.60
ST depression	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
T-wave inversion	24 (15%)	5 (11%)	8 (12%)	11 (22%)	0.24
Heart rate, bmp	76 (18)	77 (20)	78 (17)	73 (18)	0.49
Systolic BP, mm Hg	151 (27)	152 (22)	152 (31)	150 (26)	0.95
Haemoglobin, g/L	143 (15)	143 (16)	144 (14)	143 (14)	0.94
Creatine	82 (19)	79 (19)	81 (16)	86 (21)	0.21
eGFR, mL/min/1.73 m2	82 (18)	87 (18)	82 (17)	77 (16)	0.018
Total cholesterol, mmol/L	4.82 (1.18)	5.18 (0.95)	4.80 (1.27)	4.50 (1.17)	0.016
LDL cholesterol, mmol/L	2.96 (1.18)	3.30 (0.94)	2.97 (1.17)	2.66 (1.32)	0.028

Supplemental Table 2. Baseline characteristics of patients stratified by the presence or absence of obstructive coronary artery disease.

Variable	All participants, (n = 167)	No coronary artery disease, (n = 47)	Non- obstructive coronary artery disease, (n = 70)	Obstructive coronary artery disease, (n = 50)	p-value ¹
Peak troponin I concentration, ng/L	8 (6, 12)	8 (7, 13)	8 (6, 12)	8 (7, 12)	0.92
Clinical risk scores					
HEART	4 (3, 5)	3 (2, 4.50)	4 (4, 5)	5 (4, 5)	< 0.001
EDACS	17 (12, 21)	14 (10.8, 17)	17 (12, 21)	18 (14, 24)	0.002
GRACE	78 (64, 96)	62 (45, 73)	84 (67, 98)	88 (77, 108)	< 0.001
TIMI	1 (0, 2)	0 (0, 1)	1 (1, 2)	2 (1, 3)	< 0.001
PCE	0.19 (0.08, 0.36)	0.09 (0.04, 0.16)	0.20 (0.11, 0.36)	0.32 (0.16, 0.45)	< 0.001
SCORE2/OP	10.5 (5.0, 16.0)	5.0 (4.0, 9.0)	11.5 (6.0, 17.0)	15.0 (8.5, 18.8)	< 0.001

Values are median (interquartile range), n (%) or mean \pm SD. ¹ One-way ANOVA; Wilcoxon rank sum test; Fisher's exact test. BMI = body mass index; BP = blood pressure; bmp = beats per minute; CABG = coronary artery bypass grafting; CAD = coronary artery disease; ECG = electrocardiogram; EDACS = Emergency Department Assessment of Chest Pain Score; eGFR = estimated glomerular filtration rate; GRACE 2.0 = Global Registry of Acute Coronary Events version 2.0; HEART = History, ECG, Age, Risk factors, Troponin; LDL = low-density lipoprotein; PCE = pooled cohort equations; PCI = percutaneous coronary intervention; SCORE2/OP = Systematic COronary Risk Evaluation 2/Older Population; TIMI = Thrombolysis In Myocardial Infarction.

Risk Scores (Threshold)	True Positive	False Positive	True Negative	False Negative	Negative Predictive Value (95% CI)	Positive Predictive Value (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Proportion Ruled Out	AUC
HEART (<4)	47	73	44	3	93.6 (85.7 - 100)	39.4 (31.1 - 48.2)	94.0 (86.7 - 100)	37.7 (28.5 - 47.7)	28%	0.695 (0.618 - 0.772)
EDACS (<16)*	37	66	51	13	79.4 (68.4 - 89.1)	36.1 (27.5 - 45.3)	73.7 (61.0 - 85.7)	43.8 (34.5 - 52.6)	38%	0.649 (0.555 - 0.743)
GRACE 2.0 (≤88)	27	38	79	23	77.3 (69.1 - 85.1)	41.9 (30.4 - 54.2)	53.9 (39.5 - 67.5)	67.8 (59.5 - 76.1)	61%	0.693 (0.608 - 0.778)
TIMI (=0)	48	76	41	2	95.2 (87.2 - 100)	38.9 (30.6 - 47.5)	95.9 (90 - 100)	35.1 (26.3 - 44.6)	26%	0.730 (0.653 - 0.808)
PCE (<5%)	49	100	17	1	94.1 (81.2 - 100)	33.1 (26.1 - 40.4)	97.9 (93.5 - 100)	14.5 (8.5 - 21.6)	11%	0.714 (0.631 - 0.797)
SCORE2/OP (<5%)*	47	97	20	3	86.7 (71.4 - 100)	32.8 (25.2 - 40.6)	93.9 (86.8 - 100)	17.1 (10.7 - 24.8)	14%	0.714 (0.631 - 0.796)

Supplemental Table 3. Diagnostic performance of risk scores lowest thresholds for obstructive coronary artery disease

Risk Scores (Threshold)	True Positive	False Positive	True Negative	False Negative	Negative Predictive Value (95% CI)	Positive Predictive Value (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Proportion Ruled Out	AUC
HEART (<4)	100	20	27	20	57.3 (43.2 - 71.4)	83.4 (77.1 - 89.8)	83.3 (76.5 - 89.7)	57.5 (43.7 - 72.2)	28%	0.742 (0.655 - 0.829)
EDACS (<16)*	82	21	26	38	40.3 (27.3 - 52.8)	79.7 (72.0 - 87.0)	68.1 (59.8 - 76.2)	55.4 (39.5 - 69.1)	38%	0.684 (0.597 - 0.772)
GRACE 2.0 (≤88)	55	10	37	65	36.2 (26.9 - 45.9)	84.9 (75.5 - 93.0)	45.7 (36.6 - 54.4)	79.1 (66.7 - 90.2)	61%	0.714 (0.624 - 0.804)
TIMI (=0)	104	20	27	16	62.4 (48.8 - 77.3)	84.0 (77.7 - 90.4)	86.6 (80.6 - 92.0)	57.5 (42.2 - 72.7)	26%	0.784 (0.713 - 0.854)
PCE (<5%)	114	35	12	6	66.4 (44.4 - 87.5)	76.6 (69.5 - 83.3)	94.9 (90.7 - 98.4)	25.6 (13.2 - 38.6)	11%	0.754 (0.675 - 0.833)
SCORE2/OP (<5%)*	108	36	11	12	47.5 (26.3 - 68.2)	75.1 (67.9 - 81.9)	89.9 (84.1 - 95.1)	23.4 (11.1 - 36.2)	14%	0.757 (0.680 - 0.834)

Supplemental Table 4. Diagnostic performance of risk scores lowest thresholds for any coronary artery disease

Risk Scores (Threshold)	True Positive	False Positive	True Negative	False Negative	Negative Predictive Value (95% CI)	Positive Predictive Value (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Proportion Ruled Out	AUC
HEART (<4)	41	15	27	20	57.2 (43.1 - 70.7)	73.0 (61.1 - 83.6)	67.0 (55.4 - 77.8)	64.1 (50.0 - 78.4)	46%	0.701 (0.599 - 0.803)
EDACS (<16)*	38	17	25	23	51.9 (37.8 - 66.0)	68.9 (56.6 - 80.8)	62.3 (50.8 - 73.8)	59.0 (44.4 - 73.3)	47%	0.658 (0.551 - 0.764)
GRACE 2.0 (≤88)	25	6	36	36	50.0 (38.0 - 61.1)	80.7 (65.4 - 93.3)	41.1 (28.8 - 53.3)	85.7 (73.5 - 95.5)	70%	0.712 (0.611 - 0.814)
TIMI (=0)	45	15	27	16	62.7 (47.8 - 76.6)	75.0 (63.6 - 85.5)	73.6 (62.5 - 84.7)	64.3 (50.0 - 79.0)	42%	0.708 (0.615 - 0.801)
PCE (<5%)	58	31	11	3	79.2 (55.5 - 100.0)	65.1 (55.5 - 74.7)	95.3 (89.3 - 100)	25.9 (13.3 - 40.0)	14%	0.742 (0.645 - 0.838)
SCORE2/OP (<5%)*	55	32	10	6	62.6 (38.1 - 85.7)	63.3 (53.3 - 73.2)	90.2 (82.4 - 96.8)	23.9 (11.4 - 37.5)	16%	0.753 (0.659 - 0.846)

Supplemental Table 5. Diagnostic performance of risk scores lowest thresholds for any coronary artery disease in intermediate-risk patients without known previous coronary artery disease

Risk Scores (threshold)	True Positive	False Positive	True Negative	False Negative	Negative Predictive Value (95% CI)	Positive Predictive Value (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Proportion Ruled Out	AUC
HEART (<4)	15	41	44	3	93.6 (85.7 - 100.0)	26.7 (15.7 - 39.3)	83.1 (62.5 - 100)	51.8 (41.7 - 62.7)	46%	0.647 (0.543 - 0.752)
EDACS (<16)*	12	43	42	6	87.5 (78.0 - 95.8)	21.7 (11.3 - 33.3)	66.6 (42.8 - 88.0)	49.2 (38.8 - 59.6)	47%	0.641 (0.488 - 0.795)
GRACE 2.0 (≤88)	9	22	63	9	87.5 (79.4 - 94.3)	29.0 (13.3 - 46.0)	49.9 (26.3 - 73.3)	74.0 (63.5 - 82.8)	70%	0.727 (0.604 - 0.851)
TIMI (=0)	16	44	41	2	95.5 (88.6 - 100.0)	26.8 (16.1 - 37.9)	89.2 (72.7 - 100.0)	48.4 (37.6 - 59.3)	42%	0.671 (0.565 - 0.778)
PCE (<5%)	18	71	14	0	100.0 (100.0 - 100.0)	20.1 (12.2 - 28.6)	100.0 (100 - 100)	16.2 (8.5 - 24.4)	14%	0.747 (0.639 - 0.856)
SCORE2/OP (<5%)*	18	69	16	0	100.0 (100.0 - 100.0)	20.7 (12.5 - 29.5)	100.0 (100 - 100)	18.9 (11.1 - 27.7)	16%	0.746 (0.639 - 0.853)

Supplemental Table 6. Diagnostic performance of risk scores lowest thresholds for obstructive coronary artery disease in intermediaterisk patients without known previous coronary artery disease

Supplemental Figure 1. Summary of commonly used clinical risk scores and their calculations. *ARCHITECTSTAT troponin I assay; Abbott Laboratories. † The risk factors only apply to patients 18 – 50. **Undergoes equation transformation based on age. C represents a constant; BP blood pressure; yo years old; TnI Troponin I; chol cholesterol; HDL High Density Lipoprotein; ECG Electrocardiogram; HEART, History, ECG, Age, Risk factors, Troponin; EDACS, Emergency Department Assessment of Chest Pain Score; TIMI Thrombolysis In Myocardial Infarction; GRACE 2.0 Global Registry of Acute Coronary Events version 2.0; ASCVD Atherosclerosis Cardiovascular Disease; SCORE2/OP Systematic COronary Risk Evaluation 2/Older Population.

	<u>HEART</u>	EDACS	<u>TIMI</u>	<u>GRACE 2.0</u>	<u>PCE</u>	SCORE2/OP
Troponin*/ biomarker	Tnl ≤ normal limit: 0 1 - 3x normal limit: 1 >3x normal limit: 2	Tnl Ohr or 2hr > 99th %: High Risk	Tnl > 99th %: 1	Tnl > 99th %: 13 Creatine x C: 0–28	Log(Total chol) x C ^{tc} Log(HDL) x C ^H	Total chol x C ^{tc**} HDL x C ^{H**}
Risk/ History	No typical features: 0 Mixed typical/non - typical: 1 Mostly typical features: 2	†Coronary disease or risk factors ≥3: 4 Diaphoresis: 3	Risk factors ≥3:1Aspirin use:1Known CAD (stenosis≥50 %):1	Killip class: 0–44 Cardiac arrest: 30	Diabetes: 1 x C ^d Smoker: 1 x C ^s Coefficients (C ^x) change depending on Race: Black or White	Diabetes: 1 x C ^d Smoker: 1 x C ^s
Age	< 45 yo: 0 45 to 64 yo: 1 ≥65 yo: 2	18 to 45 yo: 2 46 to 85 yo: 4–18 ≥86 yo: 20	<65 yo: 0 65 to 74 yo: 2 ≥75 yo: 3	<90 yo x C: 0–98 ≥90 yo: 100	Log(Age) x Cª Log(Age) x Log(all) ^{\$}	Coefficients (C [×]) change depending of Age: <70 or ≥70
Sex Sex	-	Female: 0 Male: 6	-	-	Coefficients (C ^x) change depending on sex: Female or Male	Coefficients (C ^x) change depending of sex: Female or Male
Physiology	Normal ECG: 0 Abnormal ECG: 1 ST depression: 2	radiation: 5 Worse pain on inspiration: - 4 Pain by palpation: - 6	Severe angina: 1 ECG ST Elevation or LBBB: 1	Heart rate x C: 0–34 Systolic BP x C: 0–40 ST change: 17	Log(Systolic BP) x C ^{bpw} or C ^{bpwo} depending on treatment	Systolic BP x C ^{bp**}
Low risk Criteria	<u>Sum</u> < 4	<u>Sum</u> < 16 Negative 0 & 2h Tnl	<u>Sum</u> = 0	Equation (recalibration) < 89	Equation (recalibration) < 5%	Equation (recalibration) < 2.5% for ages < 70 < 7.5% for ages ≥ 70

Supplemental Figure 2. Required variables allocation and missing frequencies. A) Heat map of variables used for each risk score calculation. Required variables shown in blue. B) Frequency of missing values



B)

Supplemental Figure 3. Comparison of AUC performances using DeLong's Test. The heat map provides a visual representation of the statistical differences between the ROC curves for risk scores for A) any coronary artery disease and B) obstructive coronary artery disease. AUC = area under the curve.



Supplemental Figure 4. ROC analysis of risk scores for an adjudicated diagnosis of any coronary artery disease and obstructive coronary artery disease restricted to intermediate-risk patients without known previous coronary artery disease. Receiver-operating-characteristic (ROC) curves illustrating discrimination of troponin and risk scores for A) any coronary artery disease and B) obstructive coronary artery disease. AUC = area under the curve.



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