

SUPPLEMENTAL MATERIAL

High-sensitivity cardiac troponin I and the diagnosis of coronary artery disease in patients with suspected angina pectoris

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Supplementary Table 1. Baseline characteristics of biomarker sub-study and intervention arm of the SCOTHEART trial

	All Participants with CCTA	CCTA + Troponin	p-value
n	1781	937	
Age (mean (SD))	57.57 (9.47)	57.79 (9.55)	0.57
Male (%)	998 (56.0)	533 (56.9)	0.702
BMI (mean (SD))	29.63 (5.64)	29.62 (5.54)	0.985
Pre-existing CHD (%)	162 (9.1)	78 (8.3)	0.547
Hypertension (%)	612 (34.7)	336 (36.2)	0.485
Hyperlipidemia (%)	1,083 (60.8)	565 (60.3)	0.828
Diabetes mellitus (%)	196 (11.0)	98 (10.5)	0.711
Smoking habit* (%)	928 (52.1)	514 (54.9)	0.19
Family history of CHD (%)	770 (43.6)	394 (42.5)	0.629
Predicted 10-year CHD risk‡ (mean (SD))	17.9 (11.0)	18.2 (11.1)	0.407
Anginal Symptoms§ (%)			0.011
Atypical angina	436 (24.5)	221 (23.6)	
Non-anginal	687 (38.6)	317 (33.8)	
Typical angina	658 (36.9)	399 (42.6)	
Exercise ECG Performed (%)	1512 (85.1)	770 (82.3)	0.059
Normal	925 (65.2)	475 (66.2)	
Inconclusive	257 (18.1)	113 (15.7)	
Abnormal°	236 (16.6)	130 (18.1)	

CCTA, coronary computed tomography angiography; SD, standard deviation; BMI, body mass index; CHD, coronary heart disease; *Current and ex-smokers; ‡ASSIGN score; §European Society of Cardiology Criteria, ECG, electrocardiography.

Supplementary Table 2. Multi-variable predictors of obstructive coronary artery disease

Odds Ratio for Identifying Obstructive CAD on CCTA (95% CI)						
	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Log₂ (hs-cTnI)	1.71 (1.51 - 1.96)	1.39 (1.21 - 1.6)	1.35 (1.17 - 1.56)	1.35 (1.17 - 1.57)	1.3 (1.11 - 1.55)	1.27 (1.08 - 1.52)
Age		1.07 (1.05 - 1.09)	1.05 (1.03 - 1.07)	1.06 (1.03 - 1.08)	1.04 (1.02 - 1.07)	0.99 (0.97 - 1.02)
Male gender		3.86 (2.72 - 5.57)	3.88 (2.7 - 5.65)	4.04 (2.78 - 5.97)	3.67 (2.37 - 5.8)	1.64 (1.05 - 2.58)
Chest pain symptom						
Atypical angina			1.82 (1.11 - 3)	1.47 (0.88 - 2.47)	1.11 (0.61 - 2.03)	1.31 (0.73 - 2.34)
Typical angina			4.28 (2.85 - 6.53)	3.13 (2.03 - 4.9)	2.05 (1.21 - 3.49)	2.78 (1.69 - 4.62)
Diabetes mellitus				0.83 (0.48 - 1.42)	1.08 (0.56 - 2.03)	0.59 (0.31 - 1.08)
Hypertension				1.03 (0.73 - 1.46)	1.08 (0.71 - 1.62)	0.98 (0.66 - 1.45)
Hyperlipidaemia				2.43 (1.65 - 3.63)	2.16 (1.35 - 3.51)	1.8 (1.16 - 2.82)
Smoking status						
Ex-smoker				0.86 (0.58 - 1.25)	1.02 (0.65 - 1.59)	0.65 (0.42 - 1)
Current smoker				1.4 (0.87 - 2.22)	1.56 (0.9 - 2.68)	1.07 (0.62 - 1.83)
Family history of CHD				1.26 (0.89 - 1.79)	1.47 (0.97 - 2.22)	1.03 (0.69 - 1.55)
Exercise ECG result						
Inconclusive					1.1 (0.64 - 1.88)	
Abnormal					2.96 (1.77 - 4.98)	
Log₂ (Calcium score)						1.53 (1.42 - 1.65)

CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CI, confidence interval; hs-cTnI, high-sensitivity cardiac troponin I; CHD, coronary heart disease; ECG, electrocardiography.

Supplementary Table 3. Characteristics of SCOT-HEART biomarker sub-study cohort with CAD Consortium low prevalence cohort

	CAD Consortium Cohort	SCOT-HEART Biomarker Sub-study Cohort
n	4,426	937
Age, years	57.2±12	57.8±9.5
Male (%)	54.4	56.9
Typical angina (%)	17.2	42.6
Atypical angina (%)	61.0	23.6
Non-anginal symptoms (%)	21.8	33.8
≥70% stenosis on CCTA (%)	12.8	28.5

Values are percentage or mean ± standard deviation. CAD, coronary artery disease; SD, standard deviation; CA, coronary angiography; CCTA, coronary computed tomography angiography.

Supplementary Table 4. Baseline characteristics of patients with suspected angina stratified by cardiac troponin using the Abbott hs-cTnI Assay

	Cardiac troponin I concentrations by quintile (range [ng/L]) (Abbott hs-cTnI Assay)				
	Q1 [≤ 1 ng/L]	Q2 [1.1-1.9ng/L]	Q3 [2-2.5ng/L]	Q4 [2.6-4.1ng/L]	Q5 [≥ 4.2 ng/L]
n	198	188	183	178	184
Age, years	54.25 (9.40)	55.67 (10.33)	58.28 (9.05)	59.80 (9.04)	60.51 (8.68)
Male, %	62 (31.3)	103 (54.8)	104 (56.8)	123 (69.1)	139 (75.5)
Chest pain symptom, %					
Non-anginal	72 (36.4)	75 (39.9)	64 (35.0)	58 (32.6)	46 (25.0)
Atypical angina	55 (27.8)	47 (25.0)	48 (26.2)	32 (18.0)	39 (21.2)
Typical angina	71 (35.9)	66 (35.1)	71 (38.8)	88 (49.4)	99 (53.8)
BMI	29.20 (5.72)	29.68 (5.87)	29.93 (5.64)	29.57 (5.17)	29.64 (5.50)
Pre-existing CHD, %	10 (5.1)	16 (8.5)	14 (7.7)	20 (11.2)	19 (10.3)
Hypertension, %	55 (27.8)	50 (27.0)	62 (34.1)	82 (46.3)	85 (47.0)
Hyperlipidemia, %	101 (51.0)	103 (54.8)	122 (66.7)	109 (61.2)	125 (67.9)
Diabetes mellitus, %	23 (11.6)	18 (9.6)	21 (11.5)	15 (8.4)	22 (12.0)
Current smoker, %	37 (18.7)	46 (24.5)	34 (18.6)	26 (14.6)	31 (16.8)
Family history of CHD, %	89 (45.9)	93 (49.7)	83 (45.9)	67 (37.9)	62 (33.9)
10-year CHD risk*	11.00 [6.00, 18.00]	14.50 [8.75, 23.00]	16.00 [10.50, 23.00]	17.00 [13.00, 25.00]	19.00 [15.00, 28.25]

Data are mean (standard deviation), median [IQR], or value (%); BMI, body mass index; CHD, coronary heart disease.

*ASSIGN Score (see <http://assign-score.com/>)

Supplementary Table 5. Exercise electrocardiography and coronary computed tomography findings by troponin quintile using the Abbott hs-cTnI assay

	Cardiac troponin I concentrations by quintile (range [ng/L]) (Abbott hs-cTnI Assay)				
	Q1 [\leq 1ng/L]	Q2 [1.1-1.9ng/L]	Q3 [2-2.5ng/L]	Q4 [2.6-4.1ng/L]	Q5 [\geq 4.2ng/L]
n	198	188	183	178	184
Exercise ECG performed, %	171 (86.4)	159 (84.6)	143 (78.1)	142 (80.7)	144 (78.3)
Exercise ECG outcome					
Normal, %	113 (70.2)	107 (73.3)	91 (67.9)	88 (65.7)	71 (51.8)
Inconclusive, %	26 (16.1)	19 (13.0)	23 (17.2)	23 (17.2)	27 (19.7)
Abnormal, %	22 (13.7)	20 (13.7)	20 (14.9)	23 (17.2)	39 (28.5)
Coronary calcium score	0.00 [0.00, 47.00]	22.00 [0.00, 147.25]	24.00 [0.00, 201.00]	65.00 [0.25, 430.25]	151.00 [8.00, 780.50]
Coronary disease on CT					
No significant CHD, %	101 (51.5)	73 (38.8)	68 (37.2)	50 (28.1)	30 (16.4)
Non-obstructive CHD, %	71 (36.2)	77 (41.0)	69 (37.7)	62 (34.8)	65 (35.5)
Obstructive CHD, %	24 (12.2)	38 (20.2)	46 (25.1)	66 (37.1)	88 (48.1)
SSS score	0.00 [0.00, 3.00]	1.00 [0.00, 7.00]	1.00 [0.00, 7.00]	4.00 [0.00, 11.00]	7.00 [2.00, 14.00]

Data are median [IQR], or value (%); ECG, electrocardiography; IQR, interquartile range; CHD, coronary heart disease; SSS, segment stenosis score.

Supplementary Table 6. Model statistics using the Abbott hs-cTnI assay

Performance measure	CADC Model	CADC Model with troponin
Overall		
Coefficient of Discrimination	0.230	0.268
Brier score	0.161	0.155
Discrimination		
C-statistic [95% CI]	0.791 [0.760-0.822]	0.806 [0.776-0.836]*
Calibration (Hosmer-Lemeshow Test)		
Chi-square	15.35	14.06
P-value	0.053	0.080
NRI (Continuous) [95% CI]		0.537 [0.398-0.675]
NRI (Categorical) [95% CI]	N/A	0.086 [0.054-0.118]
Statistics at 10% PTP threshold		
Sensitivity	0.947	0.950
Specificity	0.371	0.434
PPV	0.372	0.398
NPV	0.946	0.957

CADC, Coronary Artery Disease Consortium; CI, confidence interval; NRI, net reclassification improvement; PTP, pre-test probability; PPV, positive predictive value; NPV, negative predictive value; *p = 0.003 that true difference in AUC is not equal to 0.

Supplementary Table 7. Net reclassification with the addition of cardiac troponin I to the CADC model (Abbott Assay)

Outcome: No Obstructive Disease					
CADC Model with cardiac troponin					
		Low Risk (<10%)	Intermediate Risk (10-90%)	High Risk (≥90%)	% Reclassified
CADC Model	Low Risk (<10%)	234	13	0	5
	Intermediate Risk (10-90%)	55	364	0	13
	High Risk (≥90%)	0	0	0	0
Outcome: Obstructive Disease					
CADC Model with cardiac troponin					
		Low Risk (<10%)	Intermediate Risk (10-90%)	High Risk (≥90%)	% Reclassified
CADC Model	Low Risk (<10%)	12	2	0	14
	Intermediate Risk (10-90%)	1	242	5	2
	High Risk (≥90%)	0	0	0	0
NRI(Continuous) [95% CI]: 0.5366 [0.3979-0.6752]					
NRI(Categorical) [95% CI]: 0.086 [0.0542-0.1177]					

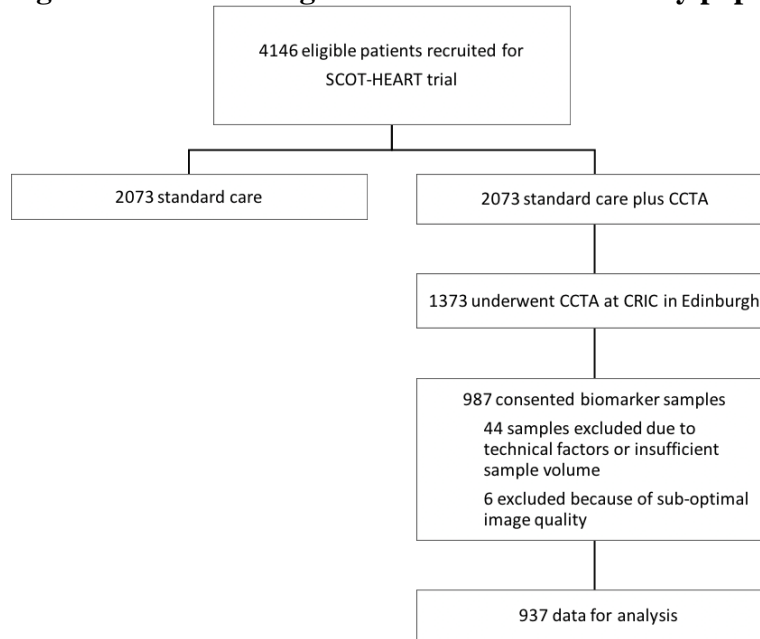
CADC, Coronary Artery Disease Consortium; NRI, net reclassification improvement; CI, confidence interval.

Supplementary Table 8. Baseline characteristics in external validation cohort stratified by cardiac troponin using the Abbott hs-cTnI Assay

Cardiac troponin I concentrations by quintile (range [ng/L]) (Abbott hs-cTnI Assay)						
	Q1 (≤3.3)	Q2 (3.4-4.0)	Q3 (4.1-4.7)	Q4 (4.8-6.8)	Q5 (>6.8)	Total Cohort
n	104	111	81	88	103	487
Age, years	53.38 (10.07)	56.30 (9.33)	58.59 (10.10)	60.74 (10.89)	62.82 (12.32)	58.24 (11.07)
Male, %	40 (38.5)	45 (40.5)	46 (56.8)	55 (62.5)	76 (73.8)	262 (53.8)
Chest pain symptom, %						
Non-anginal	32 (30.8)	29 (26.1)	25 (30.9)	23 (26.1)	29 (28.2)	138 (28.3)
Atypical angina	33 (31.7)	47 (42.3)	24 (29.6)	26 (29.5)	28 (27.2)	158 (32.4)
Typical angina	39 (37.5)	35 (31.5)	32 (39.5)	39 (44.3)	46 (44.7)	191 (39.2)
Obstructive CHD, %	8 (7.7)	15 (13.5)	11 (13.6)	20 (22.7)	40 (38.8)	94 (19.3)

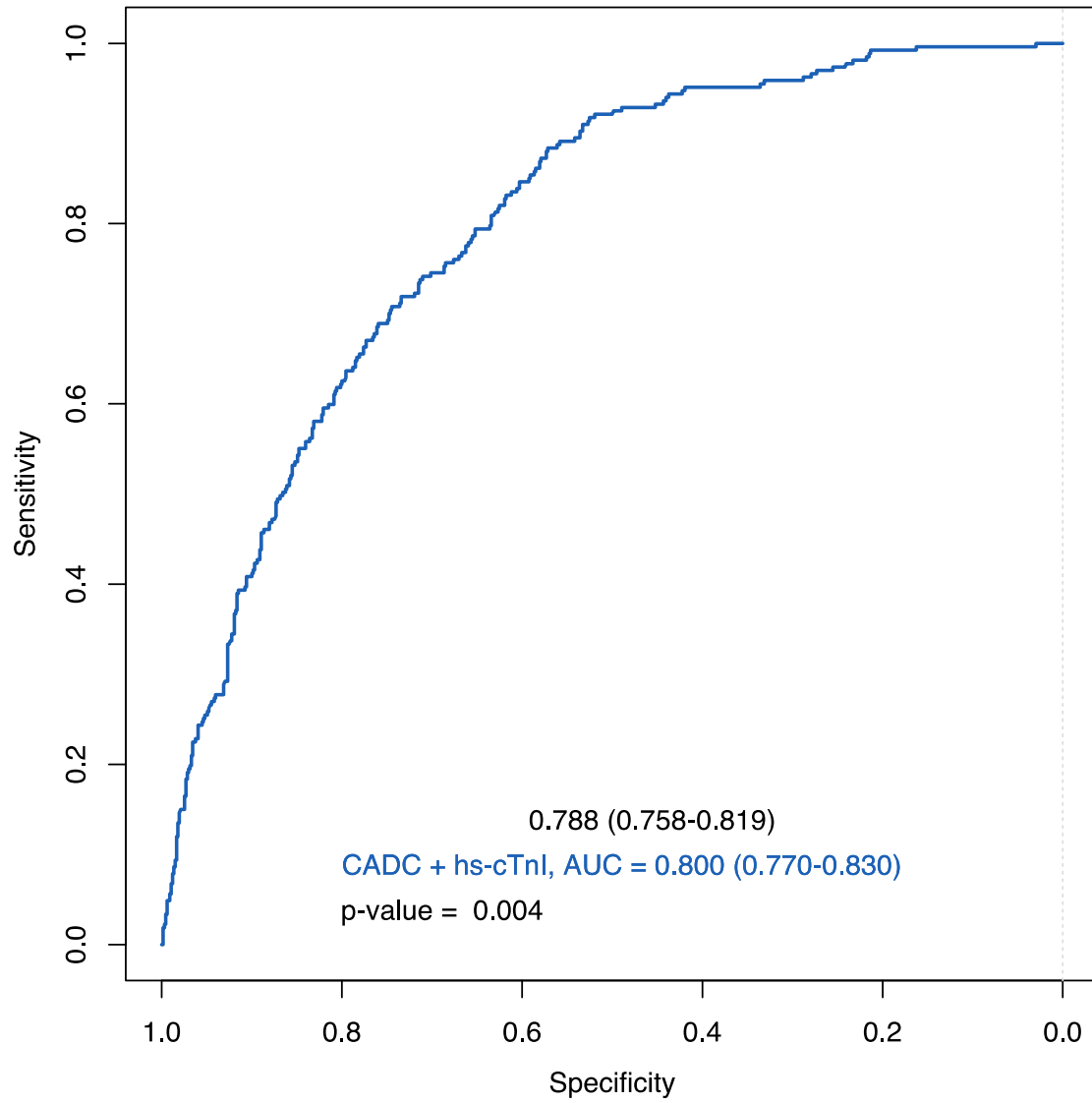
Data are mean (standard deviation), median [IQR], or value (%); CHD, coronary heart disease.

Supplementary Figure 1. Consort diagram of biomarker substudy population



CCTA, coronary computed tomography angiography; CRIC, clinical research imaging centre.

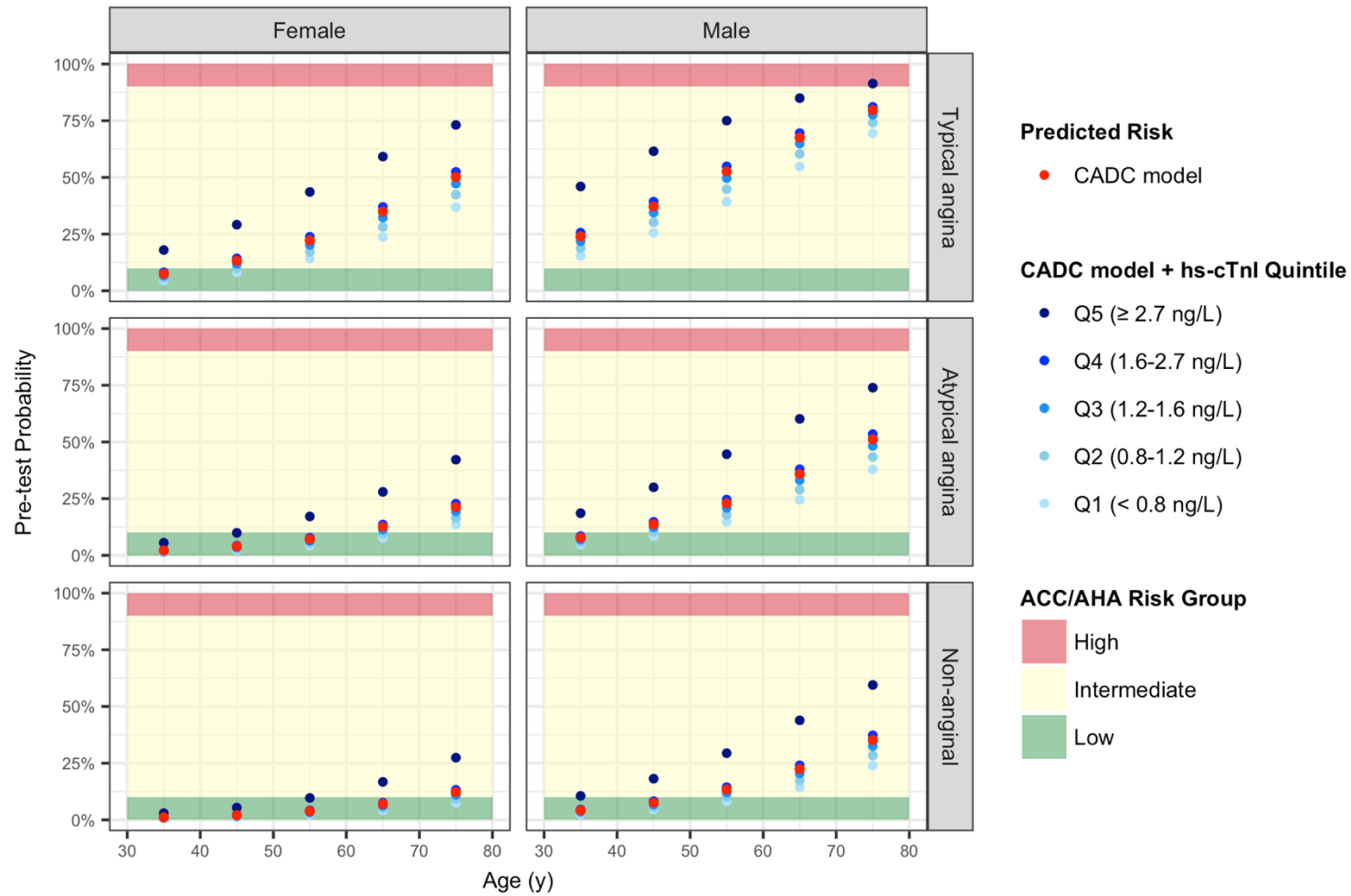
Supplementary Figure 2. Receiver operating characteristic curve for the prediction of obstructive coronary artery disease



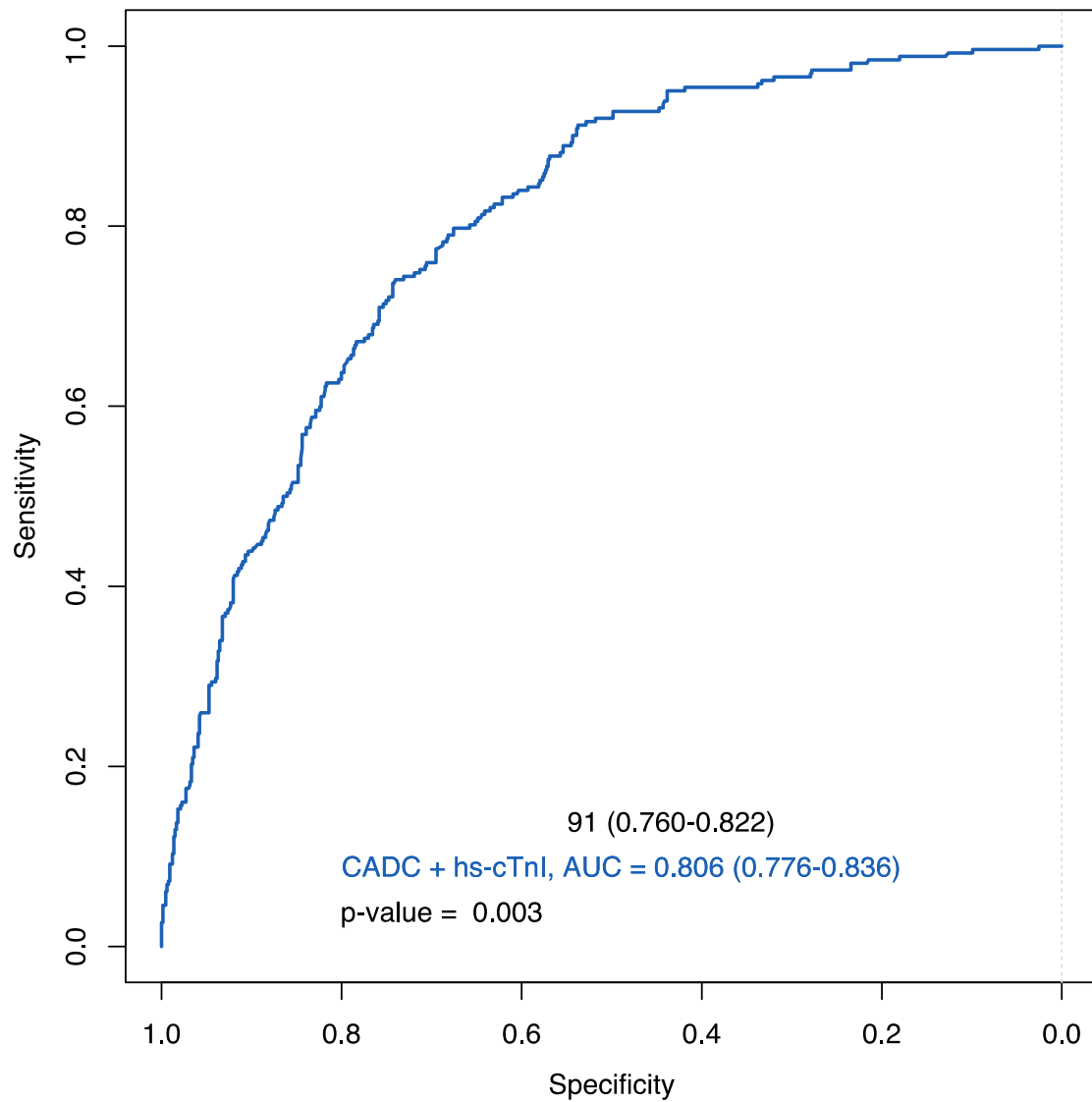
CADC, Coronary Artery Disease Consortium Risk Model; hs-cTnI, high-sensitivity cardiac troponin I; AUC, area under curve

Supplementary Figure 3. Updated Risk Model for Obstructive CAD Incorporating Troponin Quintiles (Abbott hs-cTnI Assay)

Updated Risk Model for Obstructive CAD Incorporating Troponin Quintiles (Abbott hs-cTnI Assay)

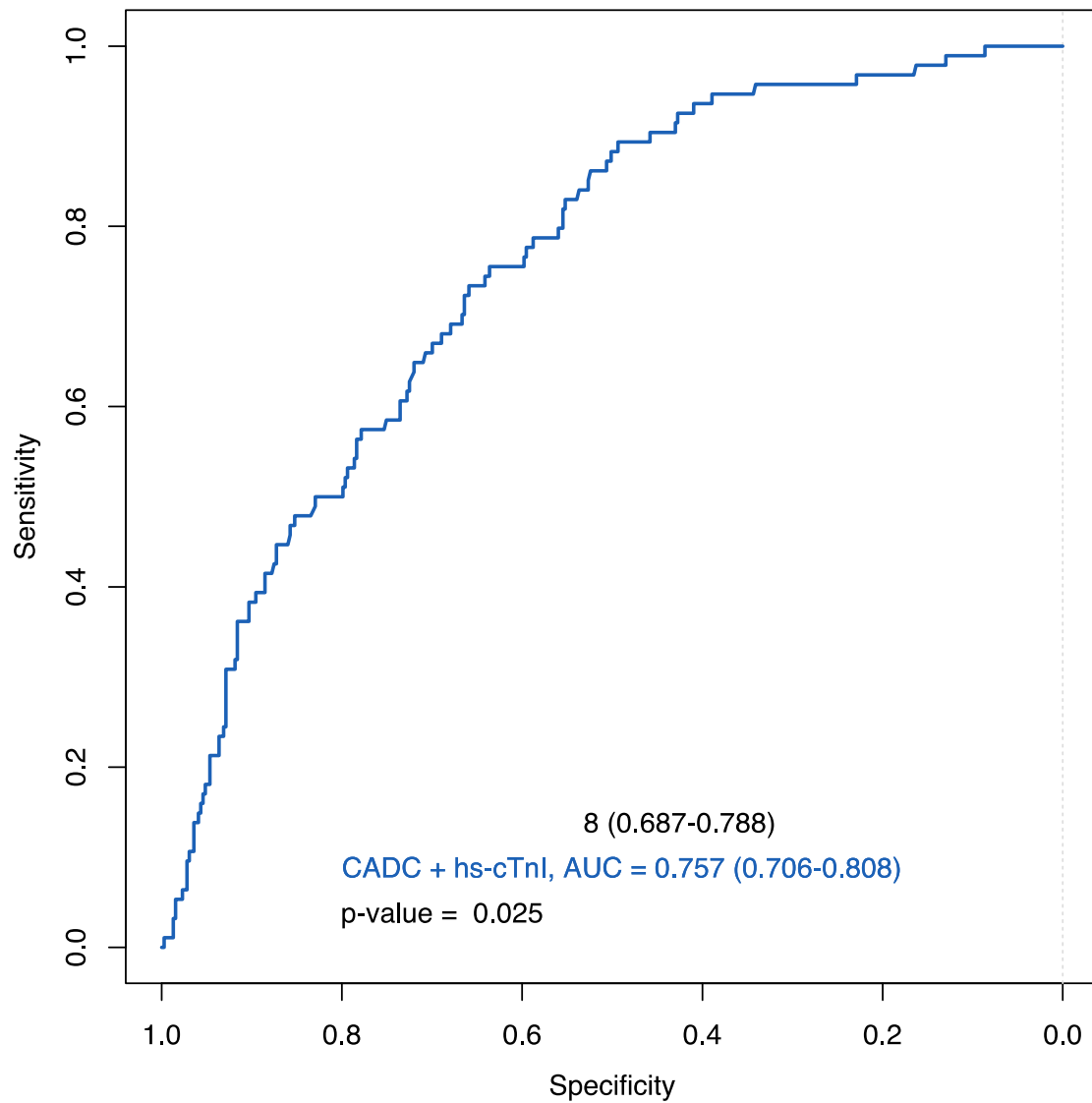


Supplementary Figure 4. Receiver operating characteristic curve for the prediction of obstructive coronary artery disease (Abbott assay)



CADC, Coronary Artery Disease Consortium Risk Model; hs-cTnI, high-sensitivity cardiac troponin I; AUC, area under curve.

Supplementary Figure 5. Receiver operating characteristic curve for the prediction of obstructive coronary artery disease in the external validation cohort (Abbott assay)



CADC, Coronary Artery Disease Consortium Risk Model; hs-cTnI, high-sensitivity cardiac troponin I; AUC, area under curve.