ORIGINAL ARTICLE

High-Sensitivity Cardiac Troponin I and the Diagnosis of Coronary Artery Disease in Patients With Suspected Angina Pectoris

See Editorial by Doust and Glasziou

BACKGROUND: We determined whether high-sensitivity cardiac troponin I can improve the estimation of the pretest probability for obstructive coronary artery disease (CAD) in patients with suspected stable angina.

METHODS AND RESULTS: In a prespecified substudy of the SCOT-HEART trial (Scottish Computed Tomography of the Heart), plasma cardiac troponin was measured using a high-sensitivity single-molecule counting assay in 943 adults with suspected stable angina who had undergone coronary computed tomographic angiography. Rates of obstructive CAD were compared with the pretest probability determined by the CAD Consortium risk model with and without cardiac troponin concentrations. External validation was undertaken in an independent study population from Denmark comprising 487 patients with suspected stable angina. Higher cardiac troponin concentrations were associated with obstructive CAD with a 5-fold increase across quintiles (9%–48%; $P<0.001$) independent of known cardiovascular risk factors (odds ratio, 1.35; 95% confidence interval, 1.25–1.46 per doubling of troponin). Cardiac troponin concentrations improved the discrimination and calibration of the CAD Consortium model for identifying obstructive CAD (C statistic, 0.788–0.800; $P=0.004$; $\chi^2=16.8$ [$P=0.032$] to 14.3 [$P=0.074$]). The updated model also improved classification of the American College of Cardiology/American Heart Association pretest probability risk categories (net reclassification improvement, 0.062; 95% confidence interval, 0.035–0.089). The revised model achieved similar improvements in discrimination and calibration when applied in the external validation cohort.

CONCLUSIONS: High-sensitivity cardiac troponin I concentration is an independent predictor of obstructive CAD in patients with suspected stable angina. Use of this test may improve the selection of patients for further investigation and treatment.

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WHAT IS KNOWN

- Most patients presenting with suspected stable angina do not ultimately have obstructive coronary artery disease identified as a cause for their symptoms.
- Despite this, current guideline-endorsed, risk-based approaches to the assessment of these patients result in the majority having to undergo noninvasive cardiac imaging tests to exclude this diagnosis.

WHAT THE STUDY ADDS

- Measuring high-sensitivity cardiac troponin concentrations in patients with suspected stable angina can safely increase the proportion of patients determined to be at low risk of coronary disease and, therefore, reduce the need for more costly imaging investigations.

Presentations with suspected stable angina are common, yet determining an accurate diagnosis is frequently challenging. Patients and clinicians alike are understandably keen to identify the cause of the symptoms in order that these can be treated and hopefully ameliorated. Of equal importance is the concern that these symptoms may reflect prognostically significant atherosclerotic disease with the associated risk of future cardiovascular events. These concerns are appropriate given that 1 in 6 patients will experience coronary death or nonfatal acute coronary syndrome in the 3 years after a diagnosis of stable angina.[1] Importantly, this risk remains substantial even in those patients with symptoms deemed noncardiac in origin.[1] Consequently, despite the central role of the clinical history and cardiovascular risk factor ascertainment in the assessment process, supplementary investigations are frequently required to provide additional certainty related to the presence or absence of obstructive coronary artery disease (CAD).[2] Several national and international bodies have proposed standardized pathways that use risk models to estimate the pretest probability (PTP) of obstructive CAD and guide decision making with regards to appropriate use of investigations.[3–5] However, there is evidence both that these models may overestimate risk[6–8] and that clinician use of stratification tools remains suboptimal.[9,10]

In light of these challenges, there is widespread interest in identifying suitable biomarkers that may improve diagnostic accuracy in patients with suspected stable CAD. As yet, no novel circulating biomarker has been shown to improve diagnostic classification.[3] It is in this context that a role may emerge for the most recent generation of high-sensitivity cardiac troponin assays. These tests offer the ability to reliably measure troponin in the majority of the healthy population and have already had a significant impact on the assessment of suspected acute coronary syndromes.[11] Meanwhile, evidence is emerging of potential roles in the context of stable cardiovascular diseases.[12,13]

This study aimed to determine whether routine quantification of plasma high-sensitivity cardiac troponin I (hs-cTnI) concentrations could improve estimation of the PTP of obstructive CAD in patients with suspected stable angina.

METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure on reasonable request to the corresponding author.

Study Design

The SCOT-HEART trial (Scottish Computed Tomography of the Heart) was a prospective, multicenter, randomized controlled study that investigated the role of coronary computed tomographic angiography (CCTA) in patients referred to a specialist clinic with suspected angina because of coronary heart disease. The study design[14] and principal findings[15] have previously been reported. Briefly, participants were recruited from 12 cardiology chest pain clinics across Scotland, and those randomized to the intervention arm underwent CCTA imaging at 1 of 3 sites in addition to routine clinical assessment. There was a prespecified biomarker substudy that obtained blood samples from those participants where the CCTA was performed at the Clinical Research Imaging Center in Edinburgh, United Kingdom. Recruitment began in November 18, 2010, and follow-up of clinical outcomes continued until June 30, 2016. The study was performed in accordance with the Declaration of Helsinki and with research ethics committee approval. Written informed consent was obtained from all individuals before study participation.

hs-cTnI Measurement

Venous blood samples for biomarker testing were obtained immediately before CCTA imaging. Blood was processed and stored at –80°C until analyzed. Plasma hs-cTnI concentrations were measured using a high-sensitivity single-molecule counting assay on the Erenna platform (Singulex, Inc, Alameda, CA), which has a limit of detection of 0.1 ng/L, a limit of quantification (coefficient of variation, <10%) of 0.4 ng/L, and a 99th centile upper reference limit of 10.9 ng/L.[16,17] To facilitate internal validation of this measurement with a clinically available assay, a secondary analysis was performed wherein the samples were analyzed using the ARCHITECT$_{STAT}$ high-sensitive troponin I assay (Abbott Laboratories, Abbott Park, IL), which has a limit of detection of 1.2 ng/L and coefficient of variation <10% at 3.0 ng/L and sex-specific 99th centile upper reference limits of 16 and 34 ng/L in women and men, respectively.[17,18]

Coronary Computed Tomographic Angiography

Participants underwent coronary artery calcium scoring and CCTA using a 320-detector scanner (Aquilion One; Toshiba Medical Systems, Nasushiobara, Japan). Computed tomographic (CT) images were analyzed by 2 trained observers with excellent reproducibility.[19] Differences in categorization were resolved by consensus. Coronary artery calcium scoring was performed using dedicated software (VScore; Vital Images, Minnetonka, MN). Agatston score was calculated using a threshold of 130 HU for each vessel and summed to give a total score. The coronary arteries were assessed using a 15-segment model with each segment classified into 1 of 5 categories dependent on the degree of luminal cross-sectional area stenosis: normal (<10% stenosis), mild nonobstructive (10%–49% stenosis), moderate nonobstructive (50%–69% stenosis), obstructive (70%–99% stenosis), or total/subtotal occlusion (100% stenosis). For the purposes of the primary outcome, obstructive CAD was defined before this analysis within the published SCOT-HEART trial protocol, as a luminal cross-sectional area stenosis of ≥70% (approximating to a 50% diameter stenosis) in at least 1 major epicardial vessel or ≥50% in the left main stem.[14] Using previously described methods,[20] the segment stenosis score was quantified as a measure of overall atherosclerotic burden. All image analyses were performed blinded to the biomarker results.

CAD Consortium Model

The CAD Consortium (CADC) is part of the European Network for the Assessment of Imaging in Medicine. In 2011 and 2012, the CADC updated and extended the earlier Diamond–Forrester model to estimate more accurately the PTP of obstructive CAD identified on invasive coronary angiography in patients with suspected stable angina.[8,21] The CADC model incorporates age, sex, and chest pain characteristics and underpins the risk tables included in the current European Society of Cardiology guideline on the management of stable CAD.[3] Furthermore, it has recently been shown to provide more accurate estimates of the probability of obstructive CAD than the modified Diamond–Forrester model currently endorsed by the American College of Cardiology/American Heart Association guidelines and appropriate use criteria for the diagnosis of stable CAD.[22–24] The American College of Cardiology/American Heart Association guideline uses 2 thresholds to stratify patients into 3 risk groups. Patients with a PTP <10% are deemed low-risk, those with a PTP between 10% and 90% are classed as intermediate risk, whereas those with a PTP ≥90% are high risk for CAD. It is widely recognized that the diagnostic use of noninvasive testing is the greatest in patients with intermediate PTP of obstructive coronary disease, and the benefits of further testing are limited in low-risk individuals. High-risk patients may warrant invasive coronary angiography for the purposes of prognostic stratification or to facilitate therapeutic revascularization.

Validation Cohort

External validation of the revised model was performed in a previously described study population[25,26] comprising 487 patients with suspected stable angina who underwent biomarker sampling in addition to coronary imaging (CCTA in 336 invasive angiographies in 151) at the Odense University Hospital, Denmark. Troponin concentrations were determined using the Abbott Architect assay.

Statistical Analysis

Statistical analysis was performed using R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Summary statistics for patient characteristics were estimated, by quintile of cardiac troponin concentration, with χ^2 and ANOVA tests being used to compare categorical and continuous variables, respectively. In logistic regression models, the probability of each patient having obstructive CAD was estimated. Cardiac troponin concentration and coronary artery calcium scores were log-transformed as linearizing transformations. Associations were estimated unadjusted and after adjusting for age, sex, chest pain characteristics, cardiovascular risk factors, and noninvasive test results. The baseline CADC model and CADC model with the addition of cardiac troponin were also fitted. In both cases, the model intercept was estimated from the sample data (with the coefficients for age, sex, and chest pain typicality fixed) to allow fair comparison of model performance. Discrimination and calibration were compared for the current CADC model and the CADC model with troponin, using the Delong method[27] and the Hosmer–Lemeshow goodness-of-fit test (*P* value <0.05 defined as poor calibration), respectively. The coefficient of discrimination (D) was calculated according to the method proposed by Tjur.[28] The categorical net reclassification improvement index was estimated using the American College of Cardiology/American Heart Association-recommended PTP threshold of 10% to distinguish low risk from intermediate or high risk. The association between troponin assays was assessed using the Pearson correlation coefficient.

The performance, in terms of discrimination and calibration, of the new model incorporating troponin concentration was also compared with the existing CADC model in an independent cohort. Neither the intercept nor the coefficients were reestimated for either model.

RESULTS

Data Collection and Study Population

The study population of the SCOT-HEART trial has previously been described.[15] Between November 18, 2010, and September 24, 2014, 4146 participants were recruited of whom 2073 were randomly assigned to standard care plus CCTA, and 1778 of these underwent CCTA at 1 of 3 sites. Blood samples were obtained from 987 participants at the time of CCTA imaging at a single center, and 943 had plasma cardiac troponin I concentrations measured. CCTA image quality was nondiagnostic in 6 cases resulting in an analysis set comprising 937 participants (Figure I in the Data Supplement). The baseline characteristics were similar between trial participants with and without estimations of troponin concentrations (Table I in the Data Supplement).

Coronary CT Angiography

The median interval between randomization and CCTA was 13 days (interquartile range [IQR], 7–18 days). The median coronary artery calcium score was 31 (IQR, 0–281) AU. CCTA demonstrated normal coronary arteries in 322 (34%), mild-to-moderate nonobstructive disease in 348 (37%), and obstructive disease in 267 (28%) participants.

hs-cTnI Concentrations

Using the Singulex assay, cardiac troponin I concentrations were above the limit of detection in 934 of 937 (99.6%) patients. The 3 samples with concentrations below this limit were assigned a value of 0.1 ng/L. The median concentration of hs-cTnI in all patients was 1.41 (IQR, 0.89–2.28) ng/L with 907 (96.8%) and 27 (2.9%) of patients above the limit of quantification (0.4 ng/L) and 99th centile upper reference limit (10.9 ng/L), respectively. The median concentration of hs-cTnI in patients with obstructive coronary disease was 1.9 (IQR, 1.3–3.1) ng/L, whereas the median concentration of hs-cTnI in those without coronary obstruction was 1.2 (IQR, 0.8–1.9) ng/L, $P<0.001$.

Higher cardiac troponin quintiles were associated with increasing age, male sex, and several cardiovascular risk factors (Table 1). The majority (82.3%) of patients underwent exercise electrocardiography, and this test was more likely to demonstrate inducible ischemia in those with higher cardiac troponin concentrations (Table 2).

Higher cardiac troponin quintiles were associated with greater coronary atherosclerotic burden as determined by coronary artery calcium score or segment stenosis score. They were also more likely to have obstructive coronary disease with a 5-fold increase between the first and fifth quintiles (9.3%–47.5%; Table 2). Each 2-fold increment in troponin concentration was associated with a 1.71-fold increment (95% confidence intervals [CIs], 1.60–1.83) in the odds of identifying obstructive CAD on CCTA. This association was moderately attenuated after adjusting for age and sex (odds ratio, 1.39; 95% CI, 1.29–1.49) but persisted on further adjustment for chest pain description, cardiovascular risk factors, exercise ECG findings, and the coronary calcium score (odds ratio, 1.27; 95% CI, 1.17–1.39; Table II in the Data Supplement).

Troponin testing with a second high-sensitivity cardiac troponin I assay (Abbott Diagnostics) was performed on 931 samples and demonstrated good agreement with the Singulex assay (r=0.88). The median troponin concentration was 2.1 ng/L (95% CI, 1.3–3.5 ng/L), and several samples reported results below the limit of detection (200; 21.5%). Despite this, the overall findings were consistent with the primary analysis (Tables IV through VIII in the Data Supplement; Figures II and III in the Data Supplement).

Table 1. Baseline Characteristics of Patients With Suspected Angina Stratified by Cardiac Troponin

	Cardiac Troponin I Concentrations by Quintile (Range, ng/L)				
	Q1 (≤0.82)	Q2 (0.83–1.16)	Q3 (1.17–1.61)	Q4 (1.62–2.66)	Q5 (>2.66)
n	193	186	183	192	183
Age, y	51.8 (9.4)	57.0 (8.3)	59.0 (9.5)	60.7 (8.8)	60.7 (8.8)
Men, %	60 (31.1)	93 (50.0)	113 (61.7)	132 (68.8)	135 (73.8)
Chest pain symptom, %					
Typical angina	54 (28.0)	64 (34.4)	81 (44.3)	101 (52.6)	99 (54.1)
Atypical angina	65 (33.7)	39 (21.0)	46 (25.1)	32 (16.7)	39 (21.3)
Nonanginal	74 (38.3)	83 (44.6)	56 (30.6)	59 (30.7)	45 (24.6)
BMI	29.6 (6.2)	29.1 (5.5)	30.1 (5.1)	30.0 (5.5)	29.4 (5.4)
Preexisting CHD, %	12 (6.2)	6 (3.2)	19 (10.4)	20 (10.4)	21 (11.5)
Hypertension, %	36 (18.7)	54 (29.3)	70 (38.5)	92 (48.7)	84 (46.4)
Hyperlipidemia, %	95 (49.2)	109 (58.6)	117 (63.9)	126 (65.6)	118 (64.5)
Diabetes mellitus, %	20 (10.4)	17 (9.1)	13 (7.1)	23 (12.0)	25 (13.7)
Current smoker, %	46 (23.8)	45 (24.2)	33 (18.0)	31 (16.2)	30 (16.4)
Family history of CHD, %	95 (50.0)	85 (46.4)	81 (44.8)	71 (37.4)	62 (34.1)
10-y CHD risk*	11.0 [6.0–16.0]	15.0 [9.0–22.8]	17.0 [11.0–24.0]	19.0 [14.0–27.0]	19.0 [14.0–27.5]

Data are mean (SD), median [IQR], or value (%). BMI indicates body mass index; CHD, coronary heart disease; and IQR, interquartile range.

*This value is determined through calculation of the ASSIGN score—a risk model derived and validated within Scotland for the determination of cardiovascular risk in patients without known coronary heart disease[37] (http://assign-score.com/).

Table 2. Exercise Electrocardiography and Coronary Computed Tomographic Findings by Troponin Quintile

	Cardiac Troponin I Concentrations by Quintile, ng/L					*P* Value
	Q1 (≤0.82)	Q2 (0.83–1.16)	Q3 (1.17–1.61)	Q4 (1.62–2.66)	Q5 (>2.66)	
Exercise ECG performed, %	162 (83.9)	161 (86.6)	153 (84.1)	149 (77.6)	145 (79.2)	0.129
Exercise ECG outcome						<0.001
Normal, %	123 (84.2)	109 (71.2)	93 (64.1)	86 (62.3)	64 (47.1)	
Inconclusive, %	11 (7.5)	24 (15.7)	23 (15.9)	26 (18.8)	29 (21.3)	
Abnormal, %	12 (8.2)	20 (13.1)	29 (20.0)	26 (18.8)	43 (31.6)	
Coronary calcium score	0.0 [0.0–31.0]	10.0 [0.0–123.00]	49.0 [0.0–316.5]	118.0 [1.8–629.3]	140.0 [4.0–739.5]	<0.001
Coronary disease on CT, %						<0.001
No significant CHD, %	107 (55.4)	78 (41.9)	55 (30.1)	44 (22.9)	37 (20.2)	
Nonobstructive CHD, %	67 (34.7)	69 (37.1)	75 (41.0)	78 (40.6)	59 (32.2)	
Obstructive CHD, %	18 (9.3)	39 (21.0)	53 (29.0)	70 (36.5)	87 (47.5)	
SSS	0.0 [0.0–2.0]	1.0 [0.0–6.0]	3.0 [0.0–10.0]	5.0 [1.0–12.0]	7.0 [1.0–14.0]	<0.001

Data are median [IQR] or value (%). CHD indicates coronary heart disease; CT, computed tomography; IQR, interquartile range; and SSS, segment stenosis score.

Update and Extension of the CADC Model

Compared with the cohort used to develop the CADC model, participants in our cohort were of similar age and more likely to have typical angina or obstructive disease on coronary imaging (Table III in the Data Supplement). Goodness-of-fit for the baseline CADC model was inadequate (χ^2=20.2; Hosmer–Lemeshow *P*=0.0095), although improved after reestimation of the model intercept (difference in deviance, 7.1; 1 degree of freedom; *P*=0.0076). Adding cardiac troponin concentrations further improved model fit (difference in deviance, 16.3; 1 degree of freedom; *P*<0.0001).

The addition of cardiac troponin concentration improved overall model performance (D=0.230–0.257; Table 3), including discrimination (C statistic, 0.788–0.800; *P*=0.0039; Figure IV in the Data Supplement). The addition of cardiac troponin concentration also improved classification of patients into American College of Cardiology/American Heart Association risk categories (Table 4; Figure 1). There was a net 10.5% (95% CI, 7.7–13.8) reduction in the number of patients determined to be at intermediate or high risk according to the CADC model but without obstructive coronary disease on CCTA. One additional patient was inappropriately reclassified as low risk who had been determined to have intermediate PTP of CAD on the original CADC model (net reclassification index, 0.062; 95% CI, 0.035–0.089).

External Validation

The validation cohort has been described previously,[25,26] and a summary of baseline characteristics is provided in Table VIII in the Data Supplement. The overall prevalence of obstructive coronary disease was 19.3%, and again, a 5-fold increase was seen across troponin quintiles. The addition of cardiac troponin concentration improved overall model performance (D=0.071–0.121), including discrimination (C statistic, 0.738–0.757;

Table 3. CADC Model Statistics

Performance Measure	CADC Model*	CADC Model With Troponin*
Overall		
Coefficient of discrimination	0.230	0.257
Brier score	0.163	0.159
Discrimination		
C statistic (95% CI)	0.788 (0.758–0.819)	0.800 (0.770–0.830)†
Calibration (Hosmer–Lemeshow test)		
χ^2	16.84	14.30
P value	0.032	0.074
NRI (categorical; 95% CI)		0.062 (0.035–0.089)
Statistics at 10% PTP threshold		
Sensitivity (95% CI)	0.944 (0.916–0.971)	0.940 (0.912–0.969); *P*=0.655
Specificity (95% CI)	0.375 (0.337–0.411)	0.440 (0.403–0.478); *P*<0.001
PPV (95% CI)	0.376 (0.339–0.412)	0.401 (0.363–0.439); *P*<0.001
NPV (95% CI)	0.944 (0.916–0.971)	0.949 (0.924–0.973); *P*=0.518

CADC indicates Coronary Artery Disease Consortium; CI, confidence interval; NPV, negative predictive value; NRI, net reclassification improvement; PPV, positive predictive value; PTP, pretest probability; and SCOT-HEART, Scottish Computed Tomography of the Heart.

*Both models apply updated intercept determined from SCOT-HEART population.

†*P*=0.0039 that true difference in area under the curve is not equal to 0.

Table 4. Net Reclassification With the Addition of Cardiac Troponin I to the CADC Model

		CADC Model With Cardiac Troponin		
		Low Risk (<10%)	Intermediate/ High Risk (≥10%)	Reclassified, %
Outcome: no obstructive disease				
CADC model	Low risk (<10%)	245	6	2
	Intermediate/ high risk (≥10%)	50	369	12
Outcome: obstructive disease				
CADC model	Low risk (<10%)	13	2	13
	Intermediate/ high risk (≥10%)	3	249	1
	NRI (categorical; 95% CI): 0.062 (0.035–0.089)			

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

P=0.025; Figure V in the Data Supplement), and model calibration (CADC model: χ^2=38.4, Hosmer–Lemeshow *P*<0.0001; CADC model, including troponin: χ^2=13.0, Hosmer–Lemeshow *P*=0.1123; Figure 2).

DISCUSSION

In the assessment of suspected stable angina, measurement of hs-cTnI improves the accuracy of the PTP of obstructive CAD as estimated using the existing guideline-endorsed CAD Consortium risk model. Applied in this manner, high-sensitivity troponin testing can appropriately reclassify 1 in 10 intermediate- or high-risk patients without obstructive disease into a low-risk category. Consequently, this simple investigation has potential to improve the appropriate use of diagnostic stress imaging tests by reducing unnecessary testing in 10.5% of those without disease. Alternatively, if the test was applied to all individuals with suspected CAD, 21 troponin tests would be required to avoid 1 unnecessary CCTA. Reassuringly, this reduction in unnecessary imaging is achieved without any decrease in the negative predictive value of the model, thereby confirming the safety of our new diagnostic approach. We have developed a risk estimation tool that incorporates cardiac troponin I concentrations to allow clinicians to improve their estimation of PTP for coronary disease (https://scotheart.highsteacs.com/)

Our study has several notable strengths. First, we chose to use a troponin assay with exceptional analytic characteristics,[17] including a diagnostic sensitivity that outperforms other available platforms and that was able to detect cardiac troponin concentrations in 99.6% of our population, and to accurately quantify cardiac troponin concentrations in 96.8% of patients. Second, because this study was nested within a larger randomized trial of CCTA imaging in patients with suspected angina, we were able to minimize the potential for case ascertainment bias that can arise when the decision to proceed to coronary imaging is dependent on clinician perception of coronary disease risk. Third, we made use of state-of-the-art CT imaging using a 320-slice scanner to define the presence and extent of CAD in all patients. Fourth, the prospective nature of this study enabled detailed and accurate phenotypic characterization of patients at baseline and comprehensive clinical follow-up. Finally, we demonstrated the external validity of the derived model in an international and independent cohort.

Current guidelines recommend a routine full blood count and measurement of renal function to identify drivers of myocardial ischemia and improve risk prediction. They also encourage analysis of lipid profiles and glycemic indices because these represent important cardiovascular risk factors. Although acknowledging that elevations in troponin have some prognostic value in stable patients, the consensus opinion in 2013[3] was that there was insufficient independent prognostic value to warrant routine measurement. This viewpoint is now being challenged by a growing body of evidence that demonstrates cardiac troponin to have independent prognostic value on several cardiovascular disorders, including heart failure and myocardial infarction, and may even be a useful indicator of therapeutic response.[12,29–31]

Overall, our findings expand on this research demonstrating that troponin concentrations predict the presence of obstructive CAD in patients with suspected stable angina. The mechanisms behind this association, including ventricular strain[32] and myocardial ischemia,[33] are now emerging. Additionally, it seems apparent from our study that atherosclerotic burden plays an important role. Whether these low concentrations of troponin reflect subclinical myocardial necrosis related to coronary plaque disruption and microvascular disease or increased myocardial cell turnover remains to be determined. To our knowledge, this is the first time a single, nongenetic[34] circulating biomarker has been shown to provide improved discrimination for the diagnosis of stable obstructive CAD beyond established risk factors. Importantly, this improvement results in successful reclassification of patients into more appropriate diagnostic probability groups, which could enable more rational use of subsequent investigations.

The high-sensitivity assay used in this study has particularly robust analytic characteristics but is presently available for research use only. We were able to measure troponin concentrations in >99% of the population across both sexes and a wide range of ages. Our

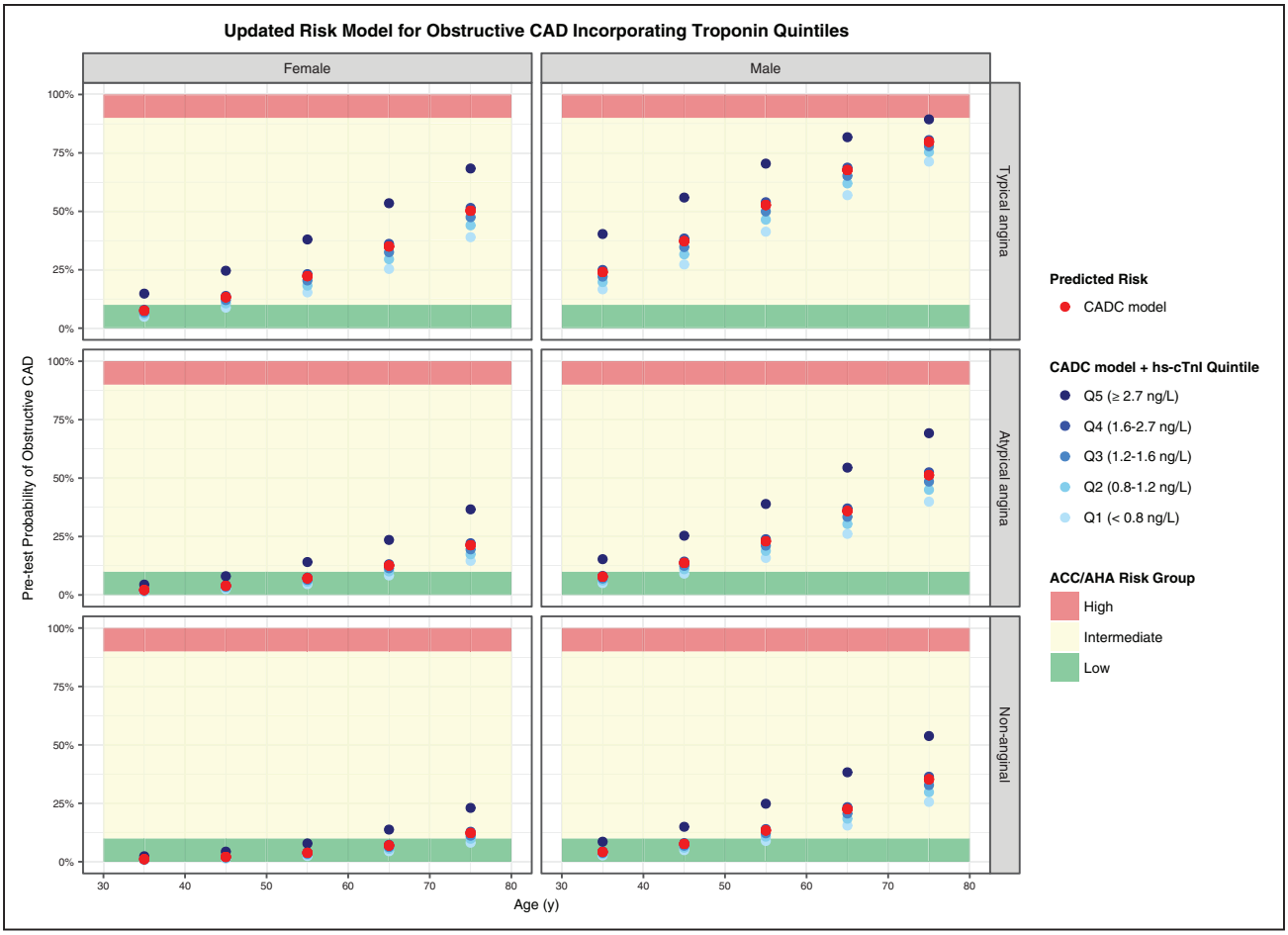

Figure 1. Cardiac troponin improves predicted risk of obstructive coronary artery disease (CAD) in patients with suspected angina.
The red dots represent the risk of obstructive CAD as estimated by the established CAD Consortium model accounting for age, sex, and symptom description. The blue dots represent the revised risk estimates with the addition of cardiac troponin quintiles. The shaded regions correspond to the risk groups and associated recommendations for further investigations as described in the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on the management of stable CAD. CADC indicates Coronary Artery Disease Consortium; and hs-cTnI, high-sensitivity cardiac troponin I.

internal validation demonstrated consistent results when using a commercially available test, but it is important to note the risk calculation will be assay specific. Whether our findings can be extrapolated to alternative clinical assays is unclear, but it would be prudent for manufacturers to validate each testing platform individually before considering use in this setting where troponin concentrations are approaching the limits of detection. Furthermore, we cannot be certain of how knowledge of troponin concentration may influence clinical management decisions because treating clinicians did not have access to the biomarker results during the conduct of the trial.

We made use of the latest generation of CT scanners developed with a focus on advancing the performance of CCTA. Although some authors may suggest that invasive coronary angiography remains the reference standard, it seems unlikely that troponin would be related to CT-defined CAD independent of the presence and extent of true CAD. As such, any misclassification is likely to be nondifferential with respect to troponin, and hence to cause us to underestimate the association between troponin and stable CAD, and the predictive performance of the model. Moreover, the chosen criteria for defining significant coronary disease on CCTA has previously been shown to correlate well with invasive angiographic findings and with noninvasively determined myocardial ischemia.[35] Indeed, in the SCOT-HEART trial, CCTA was associated with a >60% reduction in the rate of normal coronary angiography and a 30% increase in obstructive disease when downstream invasive coronary angiography was performed.[36] We also contend that a particular strength of this study arises from it being nested within a larger trial, which randomized patients to coronary imaging, thereby minimizing the case ascertainment bias inherent in earlier trials that only included patients referred for invasive coronary angiography. This applicability to the general

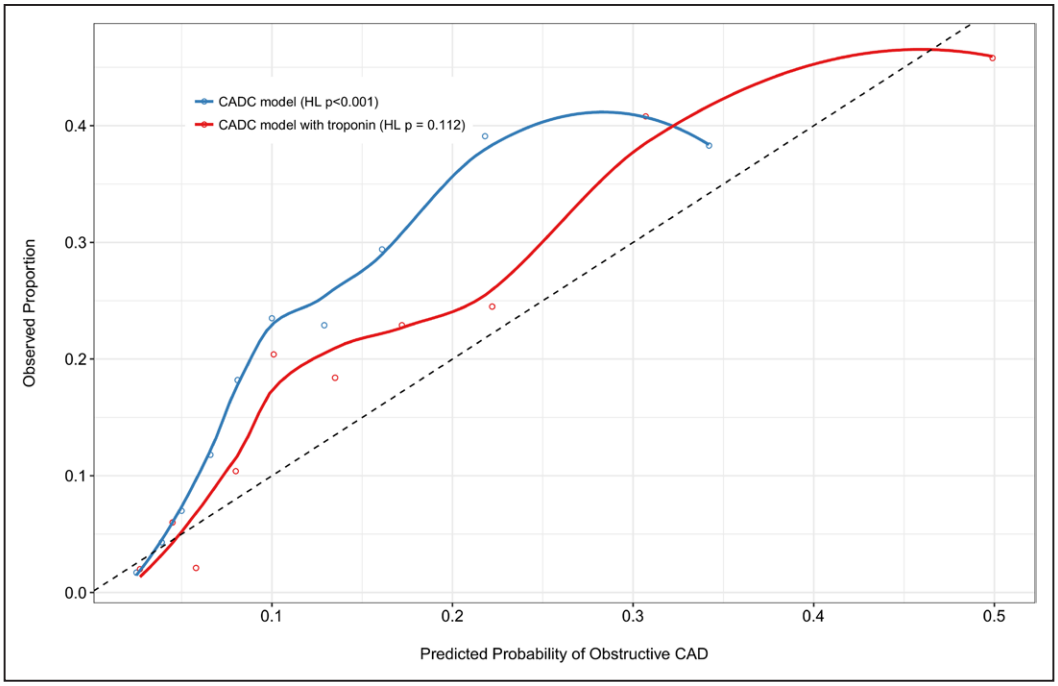

Figure 2. Model calibration within the external validation cohort.
Plot demonstrates poor calibration of predicted probability vs observed proportion of obstructive coronary artery disease (CAD) using the established CAD Consortium (CADC) model (blue). Good model calibration is demonstrated within the validation cohort after the addition of troponin to the CADC model (red). The dashed line represents perfect calibration. HL indicates Hosmer–Lemeshow.

population is reflected in the relatively lower rates of obstructive disease identified compared with previous reports.

We added a single additional continuous variable to an existing model. As such, the improvement in model performance by adding cardiac troponin is unlikely to have been substantially inflated by overfitting. Confirmation of this is demonstrated by our findings on applying the model to the external validation cohort. Indeed, it appears increasingly likely, given the potential prognostic and diagnostic information cardiac troponin offers, that indications for testing outside the acute coronary syndrome setting now exist.

CONCLUSIONS

Plasma hs-cTnI concentrations independently predict the presence of obstructive coronary disease in patients with suspected stable angina. Using this test within the chest pain clinic may improve the selection of patients for further investigation and treatment of CAD.

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DISCLOSURES

Singulex provided reagents, calibrators, and controls without charge and undertook the analysis of cardiac troponin I. Dr Mills has acted as a consultant for Abbott Laboratories, Beckman-Coulter, Roche, and Singulex. The other authors report no conflicts.

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FOOTNOTES

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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**
Log_2 (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)	
Log_2 (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, electrocardiograpy.

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

	CAD Consortium Cohort	SCOT-HEART Bio-marker 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.
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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 [≤1ng/L]	**Q2 [1.1-1.9ng/L]**	**Q3 [2-2.5ng/L]**	**Q4 [2.6-4.1ng/L]**	**Q5 [≥4.2ng/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 [≤1ng/L]	Q2 [1.1-1.9ng/L]	Q3 [2-2.5ng/L]	Q4 [2.6-4.1ng/L]	Q5 [≥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]				

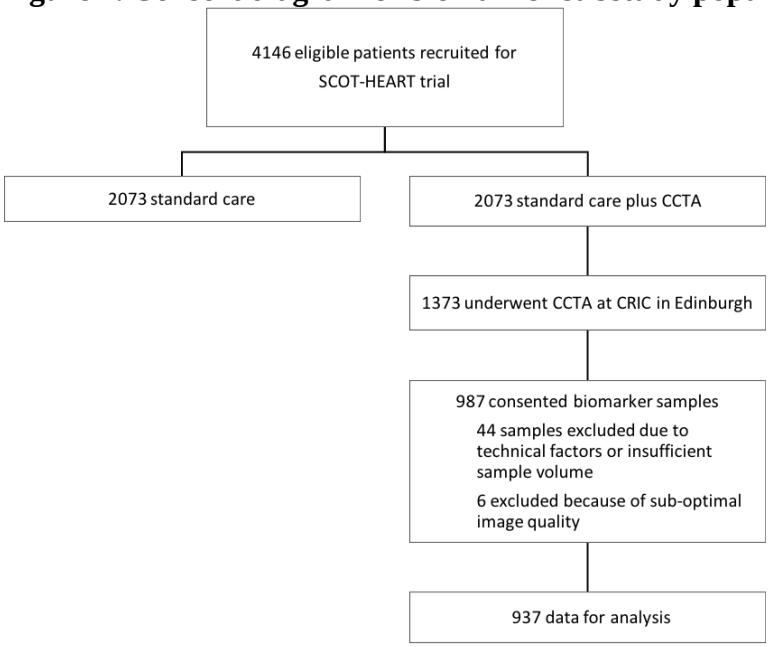
CADC, Coronary Artery Disease Consortium; NRI, net reclassification improvement; CI, confidence interval.

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)

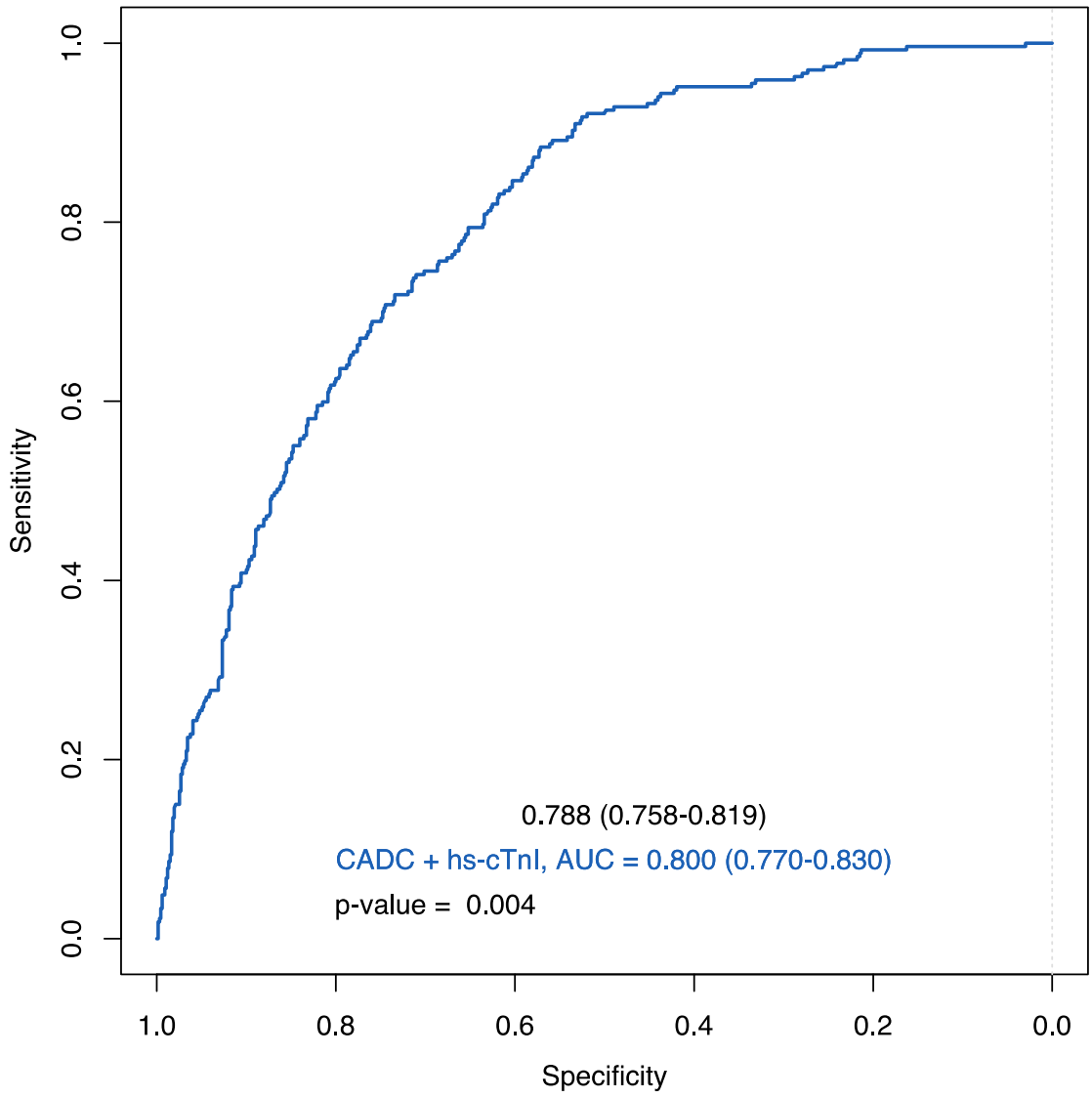
Data are mean (standard deviation), median [IQR], or value (%); CHD, coronary heart disease.

Supplementary Figure 1. Consort diagram of biomarker substudy population



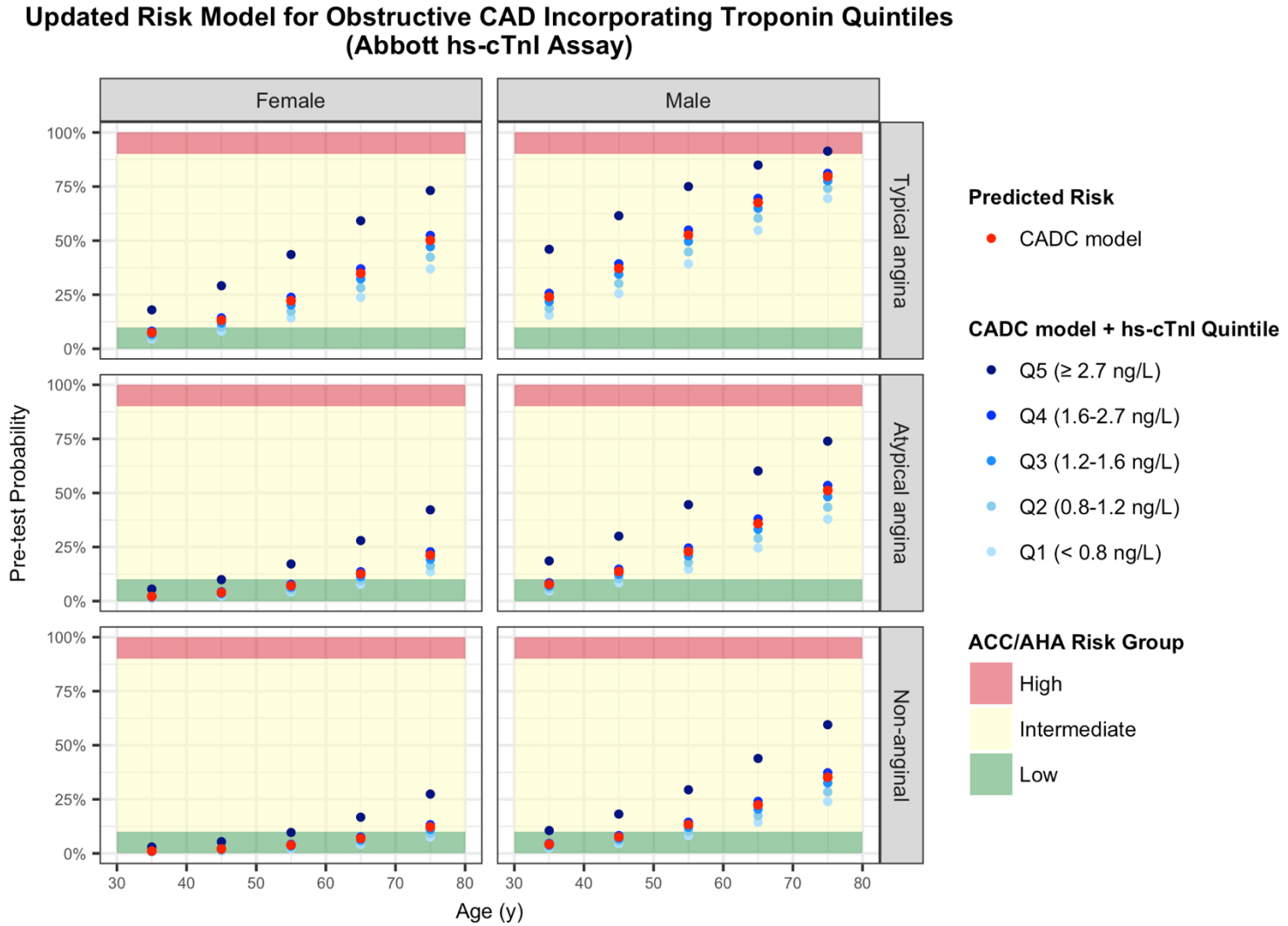
CCTA, coronary computed tomography angiography; CRIC, clinical research imaging centre.

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

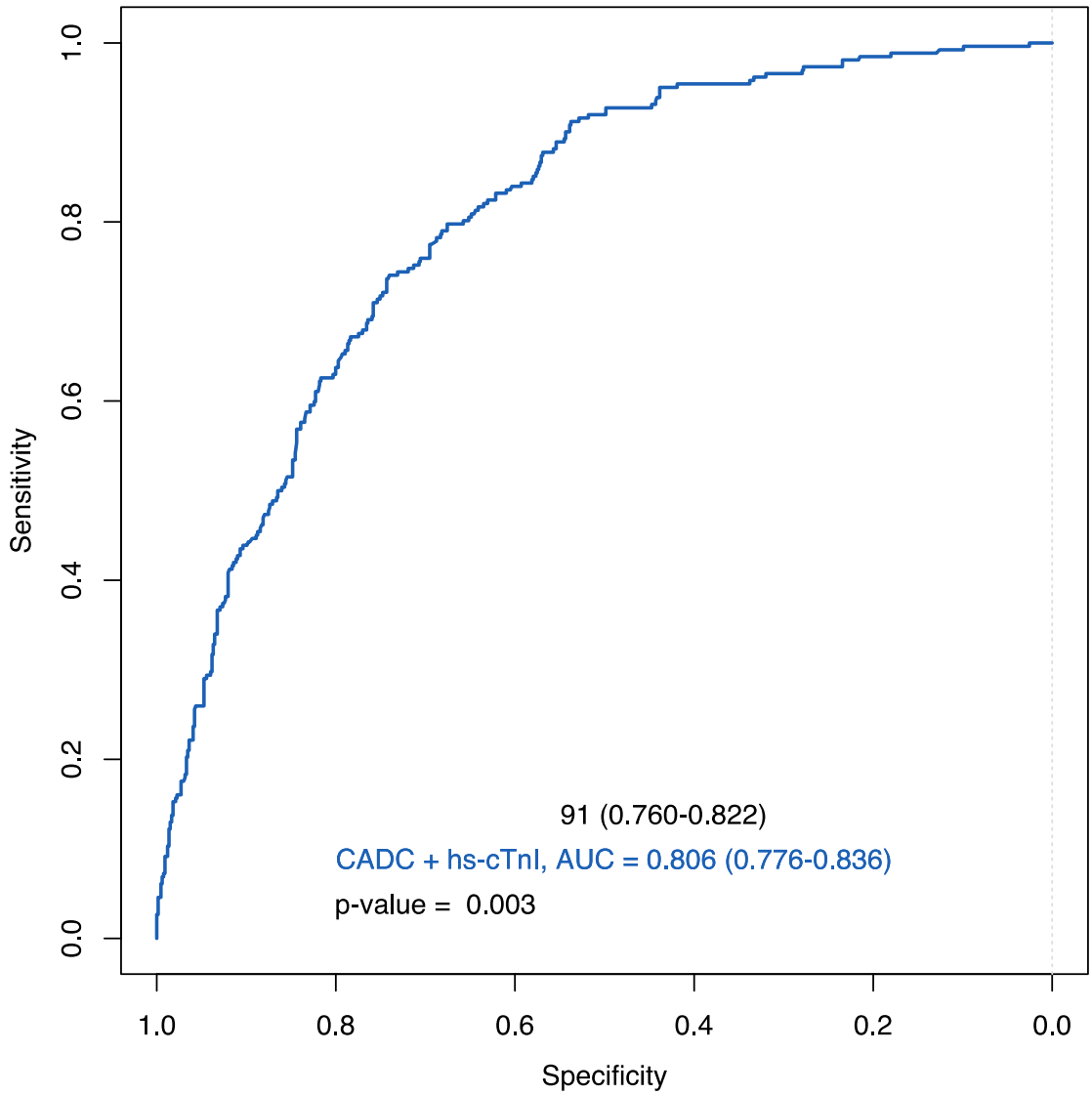


CADC, Coronary Artery Disease Consortium Risk Model; hs-cTnI, high-sensitivity cardiac troponin I; AUC, area under curve

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

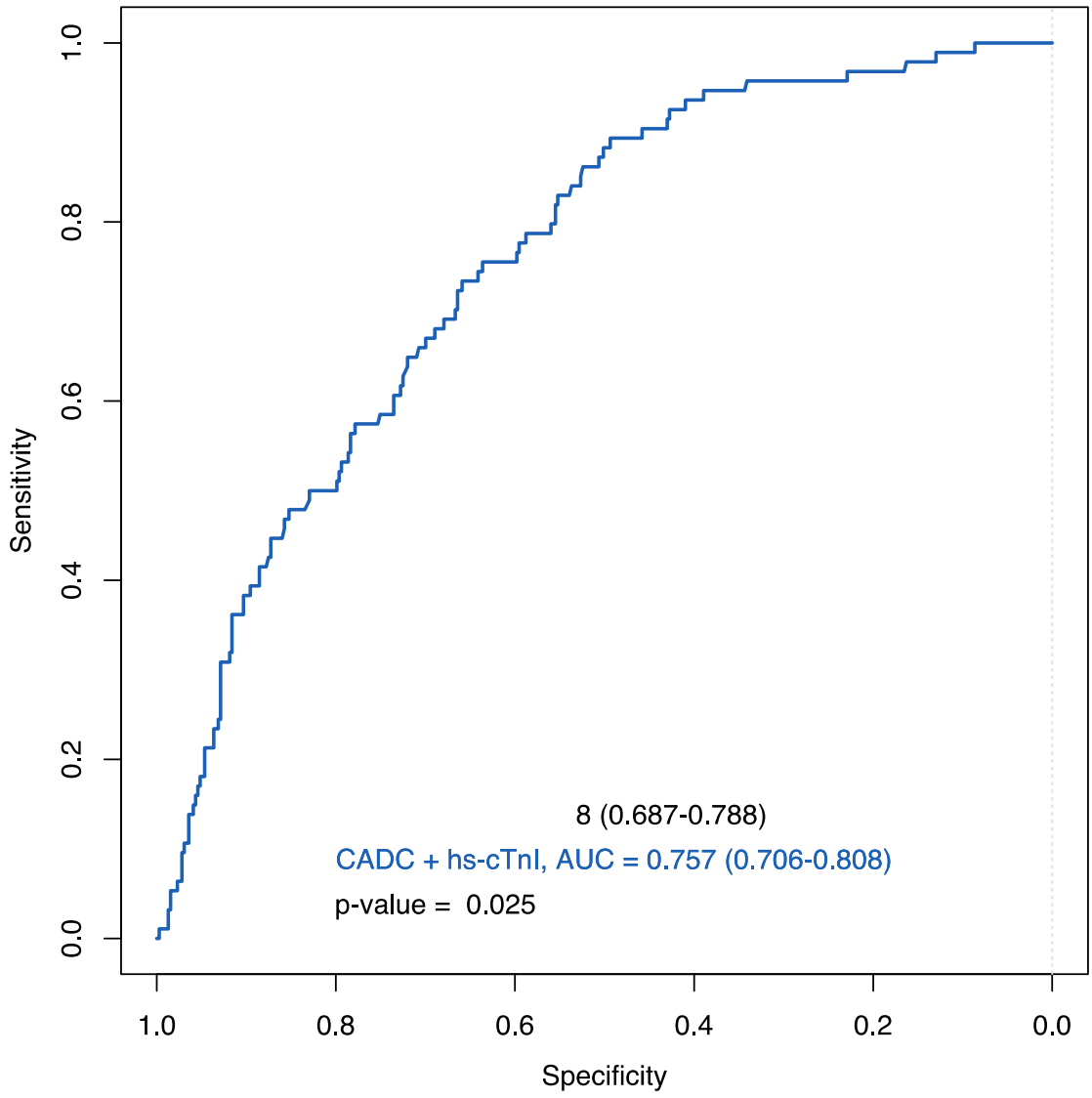


Supplementary Figure 4. Receiver operating characteristic curve for the prediction of obstructive coronary artery disease (Abbott assay)



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.