



THE UNIVERSITY *of* EDINBURGH

## Edinburgh Research Explorer

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

### Citation for published version:

Adamson, PD, Hunter, A, Madsen, DM, Shah, ASV, McAllister, DA, Pawade, TA, Williams, MC, Berry, C, Boon, NA, Flather, M, Forbes, J, McLean, S, Roditi, G, Timmis, AD, van Beek, EJR, Dweck, MR, Mickley, H, Mills, NL & Newby, DE 2018, 'High-Sensitivity Cardiac Troponin I and the Diagnosis of Coronary Artery Disease in Patients With Suspected Angina Pectoris'. *Circulation: Cardiovascular Quality and Outcomes*, vol. 11, no. 2, pp. e004227. <https://doi.org/10.1161/CIRCOUTCOMES.117.004227>

### Digital Object Identifier (DOI):

[10.1161/CIRCOUTCOMES.117.004227](https://doi.org/10.1161/CIRCOUTCOMES.117.004227)

### Link:

[Link to publication record in Edinburgh Research Explorer](#)

### Document Version:

Publisher's PDF, also known as Version of record

### Published In:

Circulation: Cardiovascular Quality and Outcomes

### Publisher Rights Statement:

Circulation: Cardiovascular Quality and Outcomes is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited.

### General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

### Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.





# 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.

**CLINICAL TRIAL REGISTRATION:** URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT01149590.

Philip D. Adamson, MD, PhD\*  
Amanda Hunter, MD\*  
Debbie M. Madsen, MB;  
Anoop S.V. Shah, MD, PhD,  
MPH  
David A. McAllister, MD  
Tania A. Pawade, MD, PhD  
Michelle C. Williams, MD, PhD  
Colin Berry, BSc, PhD  
Nicholas A. Boon, MD  
Marcus Flather, MBBS  
John Forbes, MSc, PhD  
Scott McLean, PhD  
Giles Roditi, MBChB  
Adam D. Timmis, MA, MD  
Edwin J.R. van Beek, MD, PhD  
Marc R. Dweck, MD, PhD  
Hans Mickley, MD, DSc  
Nicholas L. Mills, MD, PhD†  
David E. Newby, MD, PhD, DSc†

\*Drs Adamson and Hunter contributed equally to this work as first authors.

†Drs Mills and Newby contributed equally to this work as senior authors.

**Correspondence to:** Philip D. Adamson, MD, PhD, BHF Centre for Cardiovascular Science, University of Edinburgh, Room SU 305, Chancellor's Bldg, 49 Little France Cres, Edinburgh EH16 4SB, United Kingdom. E-mail [philip.adamson@ed.ac.uk](mailto:philip.adamson@ed.ac.uk)

**Key Words:** angina, stable ■ cohort studies ■ coronary artery disease ■ humans ■ odds ratio

© 2018 The Authors. *Circulation: Cardiovascular Quality and Outcomes* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited.

## 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.<sup>1</sup> Importantly, this risk remains substantial even in those patients with symptoms deemed noncardiac in origin.<sup>1</sup> 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).<sup>2</sup> 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.<sup>3-5</sup> However, there is evidence both that these models may overestimate risk<sup>6-8</sup> and that clinician use of stratification tools remains suboptimal.<sup>9,10</sup>

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.<sup>3</sup> 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.<sup>11</sup> Meanwhile, evidence is emerging of potential roles in the context of stable cardiovascular diseases.<sup>12,13</sup>

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<sup>14</sup> and principal findings<sup>15</sup> 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  $-80^{\circ}\text{C}$  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.<sup>16,17</sup> 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<sub>STAT</sub> 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.<sup>17,18</sup>

## 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.<sup>19</sup> 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  $\geq 70\%$  (approximating to a 50% diameter stenosis) in at least 1 major epicardial vessel or  $\geq 50\%$  in the left main stem.<sup>14</sup> Using previously described methods,<sup>20</sup> 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.<sup>8,21</sup> 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.<sup>3</sup> 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.<sup>22–24</sup> 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  $\geq 90\%$  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<sup>25,26</sup> 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  $\chi^2$  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<sup>27</sup> 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.<sup>28</sup> 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.<sup>15</sup> 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 isch-

emia 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 ( $\leq 0.82$ )	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<sup>37</sup> (<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 ( $\leq 0.82$ )	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 ( $\chi^2=20.2$ ; 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,<sup>25,26</sup> and a summary of baseline characteristics is provided in Table VIII in the [Data Supplement](#). The overall preva-

lence 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)		
$\chi^2$	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		Reclassified, %
		Low Risk (<10%)	Intermediate/High Risk (≥10%)	
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:  $\chi^2=38.4$ , Hosmer–Lemeshow  $P<0.0001$ ; CADC model, including troponin:  $\chi^2=13.0$ , 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/>)

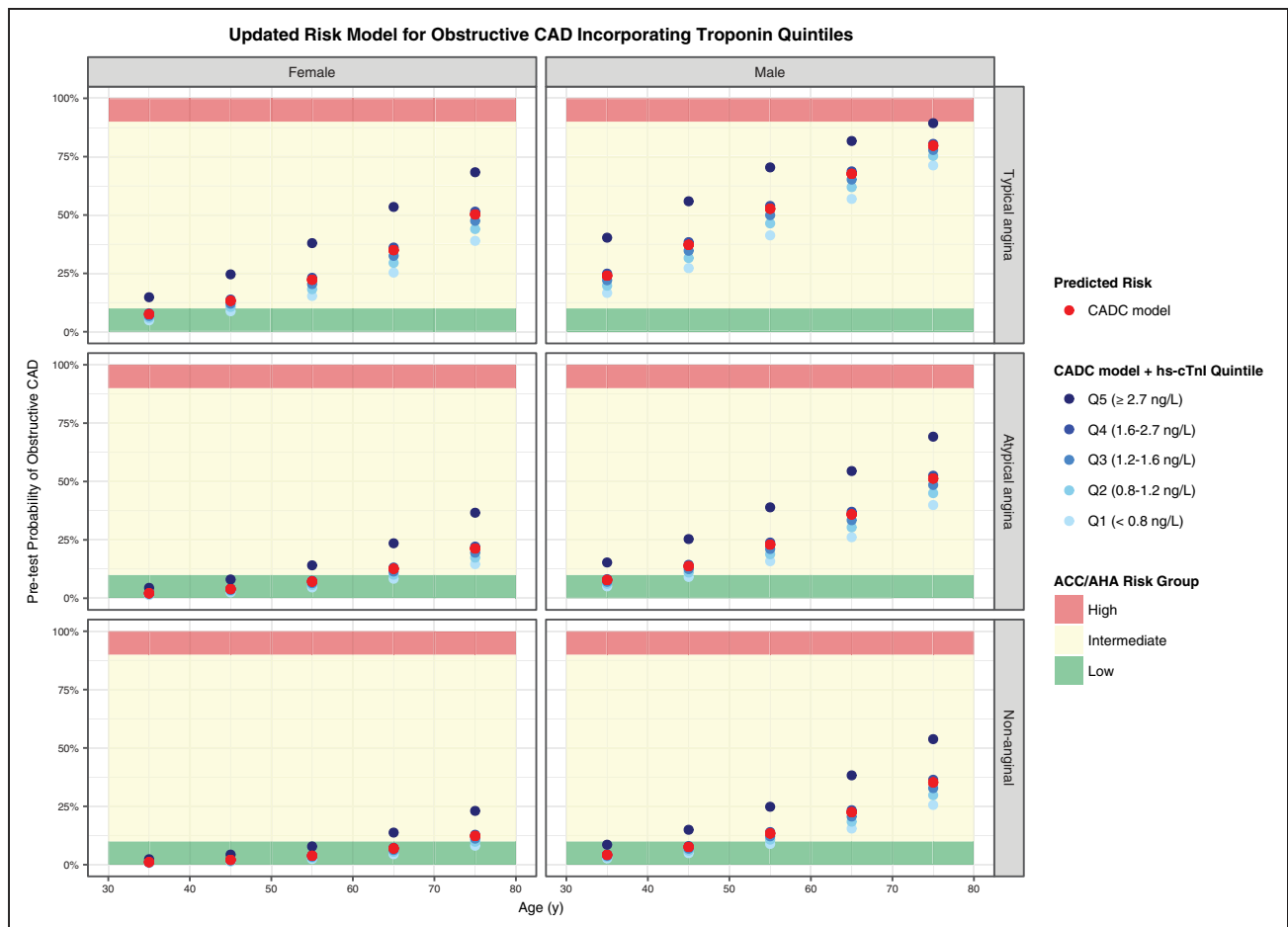
Our study has several notable strengths. First, we chose to use a troponin assay with exceptional analytic characteristics,<sup>17</sup> including a diagnostic sensitivity that outperforms other available platforms and that was able to detect cardiac troponin concentrations in 99.6%

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<sup>3</sup> 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.<sup>12,29–31</sup>

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<sup>32</sup> and myocardial ischemia,<sup>33</sup> 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<sup>34</sup> 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.**

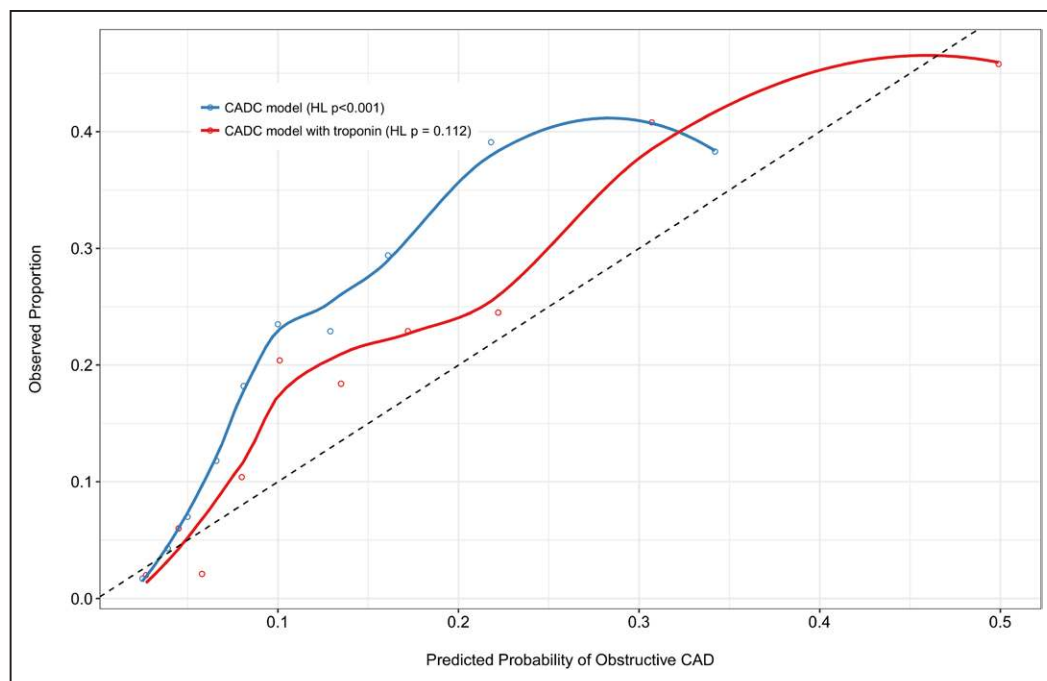
The red dots represent the risk of obstructive CAD as estimated by the established CAD Consortium model accounting for age, sex, and symptom description. The blue dots represent the revised risk estimates with the addition of cardiac troponin quintiles. The shaded regions correspond to the risk groups 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 pres-

ence 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.<sup>35</sup> 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.<sup>36</sup> 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.

## ACKNOWLEDGMENTS

We would like to thank Edwin Carter for his assistance in the preparation of samples.

## SOURCES OF FUNDING

The SCOT-HEART trial was funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorates (CZH/4/588), with supplementary awards from Edinburgh and Lothian's Health Foundation Trust and the Heart Diseases Research Fund. Drs Newby (CH/09/002; RE/13/3; RG/16/10/32375), Williams (FS/11/014), and Mills (FS/16/14/32023) are supported by the British Heart Foundation. Dr McAllister is the recipient of a Wellcome Trust Intermediate Clinical Fellowship (201492/Z/16/Z). Dr Newby is the recipient of a Wellcome Trust Senior Investigator Award (WT103782AIA). Dr van Beek is supported by the Scottish Imaging Network: A Platform of Scientific Excellence. The Royal Bank of Scotland supported the provision of 320-multidetector CT for National Health Service Lothian and the University of Edinburgh. The Clinical Research Imaging Centre (Edinburgh) is supported by the National Health Service Research Scotland through National Health Service Lothian Health Board. The research study that recruited the external validation cohort was supported by the Faculty of Health Sciences, University of Southern Denmark, and the Aase og Ejnar Danielsens Fond, Denmark.

## 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.

## AFFILIATIONS

From the British Heart Foundation Centre for Cardiovascular Science (P.D.A., A.H., A.S.V.S., T.A.P., N.A.B., E.J.R.v.B., M.R.D., N.L.M., D.E.N.) and Clinical Research Imaging Centre (M.C.W.), University of Edinburgh, United Kingdom; Department of Cardiology, Odense University Hospital, Denmark (D.M.M., H.M.); Institute of Health and Wellbeing (D.A.M.) and Institute of Clinical Sciences (C.B., G.R.), University of Glasgow, United Kingdom; Norwich Medical School, University of East Anglia, Norwich, United Kingdom (M.F.); Health Research Institute, University of Limerick, Ireland (J.F.); National Health Service, Fife, United Kingdom (S.M.); and William Harvey Research Institute, Queen Mary University of London, United Kingdom (A.D.T.).

## FOOTNOTES

Received August 24, 2017; accepted December 22, 2017.

The Data Supplement is available at <http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.117.004227/-DC1>.

*Circ Cardiovasc Qual Outcomes* is available at <http://circoutcomes.ahajournals.org>.

## REFERENCES

1. Sekhri N, Feder GS, Junghans C, Hemingway H, Timmis AD. How effective are rapid access chest pain clinics? Prognosis of incident angina and non-cardiac chest pain in 8762 consecutive patients. *Heart*. 2007;93:458–463. doi: 10.1136/hrt.2006.090894.
2. Daly CA, Clemens F, Sendon JL, Tavazzi L, Boersma E, Danchin N, Delahaye F, Gitt A, Julian D, Mulcahy D, Ruzyllo W, Thygesen K, Verheugt F, Fox KM; Euro Heart Survey Investigators. The clinical characteristics and investigations planned in patients with stable angina presenting to cardiologists in Europe: from the Euro Heart Survey of Stable Angina. *Eur Heart J*. 2005;26:996–1010. doi: 10.1093/eurheartj/ehi171.
3. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL; European Society of Cardiology Task Force; Task Force Members; ESC Committee for Practice Guidelines; Document Reviewers. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949–3003. doi: 10.1093/eurheartj/ehz296.
4. National Institute for Health and Clinical Excellence. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. *Clinical Guideline 95*. London: NICE; 2010.
5. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB III, Kligfield PD, Krumholz HM, Kwong JF, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV; American College of Cardiology Foundation. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:3097–3137. doi: 10.1161/CIR.0b013e3182776f83.
6. Almeida J, Fonseca P, Dias T, Ladeiras-Lopes R, Bettencourt N, Ribeiro J, Gama V. Comparison of Coronary Artery Disease Consortium 1 and 2 scores and Duke Clinical score to predict obstructive coronary disease by invasive coronary angiography. *Clin Cardiol*. 2016;39:223–228. doi: 10.1002/clc.22515.
7. Kumamaru KK, Arai T, Morita H, Sekine T, Takamura K, Takase S, Rybicki FJ, Kondo T. Overestimation of pretest probability of coronary artery disease by Duke clinical score in patients undergoing coronary CT angiography in a Japanese population. *J Cardiovasc Comput Tomogr*. 2014;8:198–204. doi: 10.1016/j.jcct.2014.02.002.
8. Genders TS, Steyerberg EW, Hunink MG, Nieman K, Galema TW, Mollet NR, de Feyter PJ, Krestin GP, Alkadhi H, Leschka S, Desbiolles L, Meijs MF, Cramer MJ, Knuuti J, Kajander S, Bogaert J, Goetschalckx K, Cademartiri F, Maffei E, Martini C, Seitun S, Aldrovandi A, Wildermuth S, Stinn B, Fornaro J, Feuchtner G, De Zordo T, Auer T, Plank F, Friedrich G, Pugliese F, Petersen SE, Davies LC, Schoepf UJ, Rowe GW, van Mieghem CA, van Driessche L, Sinitsyn V, Gopalan D, Nikolaou K, Bamberg F, Cury RC, Battle J, Maurovich-Horvat P, Bartykowska A, Merkely B, Becker D, Hadamitzky M, Hausleiter J, Dewey M, Zimmermann E, Laule M. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. *BMJ*. 2012;344:e3485.
9. Mudrick DW, Cowper PA, Shah BR, Patel MR, Jensen NC, Peterson ED, Douglas PS. Downstream procedures and outcomes after stress testing for chest pain without known coronary artery disease in the United States. *Am Heart J*. 2012;163:454–461. doi: 10.1016/j.ahj.2011.11.022.
10. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–895. doi: 10.1056/NEJMoa0907272.
11. Shah AS, McAllister DA, Mills R, Lee KK, Churchhouse AM, Fleming KM, Layden E, Anand A, Fersia O, Joshi NV, Walker S, Jaffe AS, Fox KA, Newby DE, Mills NL. Sensitive troponin assay and the classification of myocardial infarction. *Am J Med*. 2015;128:493.e3–501.e3. doi: 10.1016/j.amjmed.2014.10.056.
12. Everett BM, Brooks MM, Vlachos HE, Chaitman BR, Frye RL, Bhatt DL; BARI 2D Study Group. Troponin and cardiac events in stable ischemic heart and diabetes. *N Engl J Med*. 2015;373:610–620. doi: 10.1056/NEJMoa1415921.
13. Omland T, Pfeffer MA, Solomon SD, de Lemos JA, Røsjø H, Šaltytė Benth J, Maggioni A, Domanski MJ, Rouleau JL, Sabatine MS, Braunwald E; PEACE Investigators. Prognostic value of cardiac troponin I measured with a highly sensitive assay in patients with stable coronary artery disease. *J Am Coll Cardiol*. 2013;61:1240–1249. doi: 10.1016/j.jacc.2012.12.026.
14. Newby DE, Williams MC, Flapan AD, Forbes JF, Hargreaves AD, Leslie SJ, Lewis SC, McKillop G, McLean S, Reid JH, Spratt JC, Uren NG, van Beek EJ, Boon NA, Clark L, Craig P, Flather MD, McCormack C, Roditi G, Timmis AD, Krishan A, Donaldson G, Fotheringham M, Hall JF, Neary P, Cram L, Perkins S, Taylor F, Eteiba H, Rae AP, Robb K, Barrie D, Bissett K, Dawson A, Dundas S, Fogarty Y, Ramkumar PG, Houston GJ, Letham D, O'Neill L, Pringle SD, Ritchie V, Sudarshan T, Weir-McCall J, Cormack A, Findlay IN, Hood S, Murphy C, Peat E, Allen B, Baird A, Bertram D, Brian D, Cowan A, Cruden NL, Dweck MR, Flint L, Fyfe S, Keanie C, MacGillivray TJ, MacLachlan DS, MacLeod M, Mirsadraee S, Morrison A, Mills NL, Minns FC, Phillips A, Queripel LJ, Weir NW, Bett F, Divers F, Fairley K, Jacob AJ, Keegan E, White T, Gemmill J, Henry M, McGowan J, Dinnel L, Francis CM, Sandeman D, Yerramasu A, Berry C, Boylan H, Brown A, Duffy K, Froud A, Johnstone J, Lanaghan K, MacDuff R, MacLeod M, McGlynn D, McMillan N, Murdoch L, Noble C, Paterson V, Steedman T, Tzemos N; The SCOT-HEART Investigators. Role of multi-detector computed tomography in the diagnosis and management of patients attending the rapid access chest pain clinic, The Scottish computed tomography of the heart (SCOT-HEART) trial: study protocol for randomized controlled trial. *Trials*. 2012;13:184. doi: 10.1186/1745-6215-13-184.
15. SCOT-HEART Investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet*. 2015;385:2383–2391. doi: 10.1016/S0140-6736(15)60291-4.
16. Wu AH, Estis J, Helestine P, Bui K, Todd J, Kavsak P. High-sensitivity cardiac troponin I in a large community-based population at risk for cardiovascular disease. *Clin Chem*. 2015;61:S121.

17. Apple FS, Collinson PO; IFCC Task Force on Clinical Applications of Cardiac Biomarkers. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem*. 2012;58:54–61. doi: 10.1373/clinchem.2011.165795.
18. Shah AS, Griffiths M, Lee KK, McAllister DA, Hunter AL, Ferry AV, Cruikshank A, Reid A, Stoddart M, Strachan F, Walker S, Collinson PO, Apple FS, Gray AJ, Fox KA, Newby DE, Mills NL. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ*. 2015;350:g7873. doi: 10.1136/bmj.g7873.
19. Williams MC, Golay SK, Hunter A, Weir-McCall JR, Mlynska L, Dweck MR, Uren NG, Reid JH, Lewis SC, Berry C, van Beek EJ, Roditi G, Newby DE, Mirsadraee S. Observer variability in the assessment of CT coronary angiography and coronary artery calcium score: substudy of the Scottish Computed Tomography of the HEART (SCOT-HEART) trial. *Open Heart*. 2015;2:e000234. doi: 10.1136/openhrt-2014-000234.
20. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ, Lippolis NJ, Berman DS, Callister TQ. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol*. 2007;50:1161–1170. doi: 10.1016/j.jacc.2007.03.067.
21. Genders TS, Steyerberg EW, Alkadhri H, Leschka S, Desbiolles L, Nieman K, Galema TW, Meijboom WB, Mollet NR, de Feyter PJ, Cademartiri F, Maffei E, Dewey M, Zimmermann E, Laule M, Pugliese F, Barbagallo R, Sinitsyn V, Bogaert J, Goetschalckx K, Schoepf UJ, Rowe GW, Schuijf JD, Bax JJ, de Graaf FR, Knuuti J, Kajander S, van Mieghem CA, Meijs MF, Cramer MJ, Gopalan D, Feuchtnr G, Friedrich G, Krestin GP, Hunink MG; CAD Consortium. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J*. 2011;32:1316–1330. doi: 10.1093/eurheartj/ehr014.
22. Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, Kramer CM, Min JK, Patel MR, Rosenbaum L, Shaw LJ, Stainback RF, Allen JM; American College of Cardiology Foundation Appropriate Use Criteria Task Force. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society for Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;63:380–406. doi: 10.1016/j.jacc.2013.11.009.
23. Bittencourt MS, Hultén E, Polonsky TS, Hoffman U, Nasir K, Abbara S, Di Carli M, Blankstein R. European Society of Cardiology-Recommended Coronary Artery Disease Consortium pretest probability scores more accurately predict obstructive coronary disease and cardiovascular events than the diamond and forrester score: the Partners Registry. *Circulation*. 2016;134:201–211. doi: 10.1161/CIRCULATIONAHA.116.023396.
24. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB, Kligfield PD, Krumholz HM, Kwong RYK, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR, Smith SC, Spertus JA, Williams SV. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease. *Circulation*. 2012;126:e354.
25. Hosbond SE, Diederichsen AC, Saaby L, Rasmussen LM, Lambrechtsen J, Munkholm H, Sand NP, Gerke O, Poulsen TS, Mickley H. Can osteoprotegerin be used to identify the presence and severity of coronary artery disease in different clinical settings? *Atherosclerosis*. 2014;236:230–236. doi: 10.1016/j.atherosclerosis.2014.07.013.
26. Madsen DM, Diederichsen ACP, Hosbond SE, Gerke O, Mickley H. Diagnostic and prognostic value of a careful symptom evaluation and high sensitive troponin in patients with suspected stable angina pectoris without prior cardiovascular disease. *Atherosclerosis*. 2017;258:131–137. doi: 10.1016/j.atherosclerosis.2016.11.030.
27. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a non-parametric approach. *Biometrics*. 1988;44:837–845.
28. Tjur T. Coefficients of determination in logistic regression models—a new proposal: the coefficient of discrimination. *Am Stat*. 2009;63:366–372.
29. Zeller T, Tunstall-Pedoe H, Saarela O, Ojeda F, Schnabel RB, Tuovinen T, Woodward M, Struthers A, Hughes M, Kee F, Salomaa V, Kuulasmaa K, Blankenberg S; MORGAM Investigators. High population prevalence of cardiac troponin I measured by a high-sensitivity assay and cardiovascular risk estimation: the MORGAM Biomarker Project Scottish Cohort. *Eur Heart J*. 2014;35:271–281. doi: 10.1093/eurheartj/ehu406.
30. Everett BM, Zeller T, Glynn RJ, Ridker PM, Blankenberg S. High-sensitivity cardiac troponin I and B-type natriuretic peptide as predictors of vascular events in primary prevention: impact of statin therapy. *Circulation*. 2015;131:1851–1860. doi: 10.1161/CIRCULATIONAHA.114.014522.
31. Ford I, Shah AS, Zhang R, McAllister DA, Strachan FE, Caslake M, Newby DE, Packard CJ, Mills NL. High-sensitivity cardiac troponin, statin therapy, and risk of coronary heart disease. *J Am Coll Cardiol*. 2016;68:2719–2728. doi: 10.1016/j.jacc.2016.10.020.
32. Chin CW, Shah AS, McAllister DA, Joanna Cowell S, Alam S, Langrish JP, Strachan FE, Hunter AL, Maria Choy A, Lang CC, Walker S, Boon NA, Newby DE, Mills NL, Dweck MR. High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis. *Eur Heart J*. 2014;35:2312–2321. doi: 10.1093/eurheartj/ehu189.
33. Lee G, Twerenbold R, Tanglay Y, Reichlin T, Honegger U, Wagener M, Jaeger C, Rubini Gimenez M, Hochgruber T, Puelacher C, Radosavac M, Kreutzinger P, Stallone F, Hillinger P, Krivoshei L, Herrmann T, Mayr R, Freese M, Wild D, Rentsch KM, Todd J, Osswald S, Zellweger MJ, Mueller C. Clinical benefit of high-sensitivity cardiac troponin I in the detection of exercise-induced myocardial ischemia. *Am Heart J*. 2016;173:8–17. doi: 10.1016/j.ahj.2015.11.010.
34. Thomas GS, Voros S, McPherson JA, Lansky AJ, Winn ME, Bateman TM, Elashoff MR, Lieu HD, Johnson AM, Daniels SE, Ladapo JA, Phelps CE, Douglas PS, Rosenberg S. A blood-based gene expression test for obstructive coronary artery disease tested in symptomatic nondiabetic patients referred for myocardial perfusion imaging the COMPASS study. *Circ Cardiovasc Genet*. 2013;6:154–162. doi: 10.1161/CIRCGENETICS.112.964015.
35. Gaemperli O, Schepis T, Valenta I, Koepfli P, Husmann L, Scheffel H, Leschka S, Eberli FR, Luscher TF, Alkadhri H, Kaufmann PA. Functionally relevant coronary artery disease: comparison of 64-section CT angiography with myocardial perfusion SPECT. *Radiology*. 2008;248:414–423. doi: 10.1148/radiol.2482071307.
36. Williams MC, Hunter A, Shah ASV, Assi V, Lewis S, Smith J, Berry C, Boon NA, Clark E, Flather M, Forbes J, McLean S, Roditi G, van Beek EJ, Timmis AD, Newby DE; SCOT-HEART Investigators. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol*. 2016;67:1759–1768. doi: 10.1016/j.jacc.2016.02.026.
37. Woodward M, Brindle P, Tunstall-Pedoe H; SIGN Group on Risk Estimation. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart*. 2007;93:172–176. doi: 10.1136/hrt.2006.108167.

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

Philip D. Adamson, Amanda Hunter, Debbie M. Madsen, Anoop S.V. Shah, David A. McAllister, Tania A. Pawade, Michelle C. Williams, Colin Berry, Nicholas A. Boon, Marcus Flather, John Forbes, Scott McLean, Giles Roditi, Adam D. Timmis, Edwin J.R. van Beek, Marc R. Dweck, Hans Mickley, Nicholas L. Mills and David E. Newby

*Circ Cardiovasc Qual Outcomes.* 2018;11:

doi: 10.1161/CIRCOUTCOMES.117.004227

*Circulation: Cardiovascular Quality and Outcomes* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2018 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circoutcomes.ahajournals.org/content/11/2/e004227>

Free via Open Access

Data Supplement (unedited) at:

<http://circoutcomes.ahajournals.org/content/suppl/2018/01/17/CIRCOUTCOMES.117.004227.DC1>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Quality and Outcomes* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:

<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Circulation: Cardiovascular Quality and Outcomes* is online at:

<http://circoutcomes.ahajournals.org/subscriptions/>

## SUPPLEMENTAL MATERIAL

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

Philip D. Adamson\*<sup>1</sup>, Amanda Hunter\*<sup>1</sup>, Debbie M. Madsen<sup>2</sup>, Anoop S.V. Shah<sup>1</sup>, David A. McAllister<sup>3</sup>, Tania A. Pawade<sup>1</sup>, Michelle C. Williams<sup>4</sup>, Colin Berry<sup>5</sup>, Nicholas A. Boon<sup>1</sup>, Marcus Flather<sup>6</sup>, John Forbes<sup>7</sup>, Scott McLean<sup>8</sup>, Giles Roditi<sup>5</sup>, Adam D. Timmis<sup>9</sup>, Edwin J.R. van Beek<sup>1,4</sup>, Marc R. Dweck<sup>1</sup>, Hans Mickley<sup>2</sup>, Nicholas L. Mills\*\*<sup>1</sup> and David E. Newby\*\*<sup>1</sup>.

<sup>1</sup>BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom

<sup>2</sup>Department of Cardiology, Odense University Hospital, Odense C, Denmark

<sup>3</sup>Institute of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom

<sup>4</sup>Clinical Research Imaging Centre, University of Edinburgh, Edinburgh, United Kingdom

<sup>5</sup>Institute of Clinical Sciences, University of Glasgow, Glasgow, United Kingdom

<sup>6</sup>Norwich Medical School, University of East Anglia, Norwich, United Kingdom

<sup>7</sup>Health Research Institute, University of Limerick, Limerick, Ireland

<sup>8</sup>National Health Service, Fife, United Kingdom

<sup>9</sup>William Harvey Research Institute, Queen Mary University of London, London, United Kingdom

\*Drs Adamson and Hunter contributed equally to this work.

\*\*Equal contribution

### Correspondence to:

Dr Philip D. Adamson

Room SU 305

BHF Centre for Cardiovascular Science

Chancellor's Building

University of Edinburgh

49 Little France Cres

Edinburgh

EH16 4SB

UNITED KINGDOM

Email: [philip.adamson@ed.ac.uk](mailto:philip.adamson@ed.ac.uk)

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

	All Participants with CCTA	CCTA + Troponin	p-value
<b>n</b>	1781	937	
<b>Age (mean (SD))</b>	57.57 (9.47)	57.79 (9.55)	0.57
<b>Male (%)</b>	998 (56.0)	533 (56.9)	0.702
<b>BMI (mean (SD))</b>	29.63 (5.64)	29.62 (5.54)	0.985
<b>Pre-existing CHD (%)</b>	162 (9.1)	78 (8.3)	0.547
<b>Hypertension (%)</b>	612 (34.7)	336 (36.2)	0.485
<b>Hyperlipidemia (%)</b>	1,083 (60.8)	565 (60.3)	0.828
<b>Diabetes mellitus (%)</b>	196 (11.0)	98 (10.5)	0.711
<b>Smoking habit* (%)</b>	928 (52.1)	514 (54.9)	0.19
<b>Family history of CHD (%)</b>	770 (43.6)	394 (42.5)	0.629
<b>Predicted 10-year CHD risk‡ (mean (SD))</b>	17.9 (11.0)	18.2 (11.1)	0.407
<b>Anginal Symptoms§ (%)</b>			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)	
<b>Exercise ECG Performed (%)</b>	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**

<b>Odds Ratio for Identifying Obstructive CAD on CCTA (95% CI)</b>						
	<b>Model 1</b>	<b>Model 2</b>	<b>Model 3</b>	<b>Model 4</b>	<b>Model 5</b>	<b>Model 6</b>
<b>Log<sub>2</sub> (hs-cTnI)</b>	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 )
<b>Age</b>		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 )
<b>Male gender</b>		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 )
<b>Chest pain symptom</b>						
<b>Atypical angina</b>			1.82 ( 1.11 - 3 )	1.47 ( 0.88 - 2.47 )	1.11 ( 0.61 - 2.03 )	1.31 ( 0.73 - 2.34 )
<b>Typical angina</b>			4.28 ( 2.85 - 6.53 )	3.13 ( 2.03 - 4.9 )	2.05 ( 1.21 - 3.49 )	2.78 ( 1.69 - 4.62 )
<b>Diabetes mellitus</b>				0.83 ( 0.48 - 1.42 )	1.08 ( 0.56 - 2.03 )	0.59 ( 0.31 - 1.08 )
<b>Hypertension</b>				1.03 ( 0.73 - 1.46 )	1.08 ( 0.71 - 1.62 )	0.98 ( 0.66 - 1.45 )
<b>Hyperlipidaemia</b>				2.43 ( 1.65 - 3.63 )	2.16 ( 1.35 - 3.51 )	1.8 ( 1.16 - 2.82 )
<b>Smoking status</b>						
<b>Ex-smoker</b>				0.86 ( 0.58 - 1.25 )	1.02 ( 0.65 - 1.59 )	0.65 ( 0.42 - 1 )
<b>Current smoker</b>				1.4 ( 0.87 - 2.22 )	1.56 ( 0.9 - 2.68 )	1.07 ( 0.62 - 1.83 )
<b>Family history of CHD</b>				1.26 ( 0.89 - 1.79 )	1.47 ( 0.97 - 2.22 )	1.03 ( 0.69 - 1.55 )
<b>Exercise ECG result</b>						
<b>Inconclusive</b>					1.1 ( 0.64 - 1.88 )	
<b>Abnormal</b>					2.96 ( 1.77 - 4.98 )	
<b>Log<sub>2</sub> (Calcium score)</b>						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**

	<b>CAD Consortium Cohort</b>	<b>SCOT-HEART Biomarker Sub-study Cohort</b>
<b>n</b>	4,426	937
<b>Age, years</b>	57.2±12	57.8±9.5
<b>Male (%)</b>	54.4	56.9
<b>Typical angina (%)</b>	17.2	42.6
<b>Atypical angina (%)</b>	61.0	23.6
<b>Non-anginal symptoms (%)</b>	21.8	33.8
<b>≥70% stenosis on CCTA (%)</b>	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 [ $\leq 1$ ng/L]	Q2 [1.1-1.9ng/L]	Q3 [2-2.5ng/L]	Q4 [2.6-4.1ng/L]	Q5 [ $\geq 4.2$ ng/L]
<b>n</b>	198	188	183	178	184
<b>Age, years</b>	54.25 (9.40)	55.67 (10.33)	58.28 (9.05)	59.80 (9.04)	60.51 (8.68)
<b>Male, %</b>	62 (31.3)	103 (54.8)	104 (56.8)	123 (69.1)	139 (75.5)
<b>Chest pain symptom, %</b>					
<b>Non-anginal</b>	72 (36.4)	75 (39.9)	64 (35.0)	58 (32.6)	46 (25.0)
<b>Atypical angina</b>	55 (27.8)	47 (25.0)	48 (26.2)	32 (18.0)	39 (21.2)
<b>Typical angina</b>	71 (35.9)	66 (35.1)	71 (38.8)	88 (49.4)	99 (53.8)
<b>BMI</b>	29.20 (5.72)	29.68 (5.87)	29.93 (5.64)	29.57 (5.17)	29.64 (5.50)
<b>Pre-existing CHD, %</b>	10 (5.1)	16 (8.5)	14 (7.7)	20 (11.2)	19 (10.3)
<b>Hypertension, %</b>	55 (27.8)	50 (27.0)	62 (34.1)	82 (46.3)	85 (47.0)
<b>Hyperlipidemia, %</b>	101 (51.0)	103 (54.8)	122 (66.7)	109 (61.2)	125 (67.9)
<b>Diabetes mellitus, %</b>	23 (11.6)	18 (9.6)	21 (11.5)	15 (8.4)	22 (12.0)
<b>Current smoker, %</b>	37 (18.7)	46 (24.5)	34 (18.6)	26 (14.6)	31 (16.8)
<b>Family history of CHD, %</b>	89 (45.9)	93 (49.7)	83 (45.9)	67 (37.9)	62 (33.9)
<b>10-year CHD risk*</b>	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 [ $\leq 1$ ng/L]	Q2 [1.1-1.9ng/L]	Q3 [2-2.5ng/L]	Q4 [2.6-4.1ng/L]	Q5 [ $\geq 4.2$ ng/L]
<b>n</b>	198	188	183	178	184
<b>Exercise ECG performed, %</b>	171 (86.4)	159 (84.6)	143 (78.1)	142 (80.7)	144 (78.3)
<b>Exercise ECG outcome</b>					
<b>Normal, %</b>	113 (70.2)	107 (73.3)	91 (67.9)	88 (65.7)	71 (51.8)
<b>Inconclusive, %</b>	26 (16.1)	19 (13.0)	23 (17.2)	23 (17.2)	27 (19.7)
<b>Abnormal, %</b>	22 (13.7)	20 (13.7)	20 (14.9)	23 (17.2)	39 (28.5)
<b>Coronary calcium score</b>	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]
<b>Coronary disease on CT</b>					
<b>No significant CHD, %</b>	101 (51.5)	73 (38.8)	68 (37.2)	50 (28.1)	30 (16.4)
<b>Non-obstructive CHD, %</b>	71 (36.2)	77 (41.0)	69 (37.7)	62 (34.8)	65 (35.5)
<b>Obstructive CHD, %</b>	24 (12.2)	38 (20.2)	46 (25.1)	66 (37.1)	88 (48.1)
<b>SSS score</b>	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
<b>Overall</b>		
<b>Coefficient of Discrimination</b>	0.230	0.268
<b>Brier score</b>	0.161	0.155
<b>Discrimination</b>		
<b>C-statistic [95% CI]</b>	0.791 [0.760-0.822]	0.806 [0.776-0.836]*
<b>Calibration (Hosmer-Lemeshow Test)</b>		
<b>Chi-square</b>	15.35	14.06
<b>P-value</b>	0.053	0.080
<b>NRI (Continuous) [95% CI]</b>		0.537 [0.398-0.675]
<b>NRI (Categorical) [95% CI]</b>	N/A	0.086 [0.054-0.118]
<b>Statistics at 10% PTP threshold</b>		
<b>Sensitivity</b>	0.947	0.950
<b>Specificity</b>	0.371	0.434
<b>PPV</b>	0.372	0.398
<b>NPV</b>	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)**

<b>Outcome: No Obstructive Disease</b>					
		<b>CADC Model with cardiac troponin</b>			
		Low Risk (<10%)	Intermediate Risk (10-90%)	High Risk (≥90%)	% Reclassified
<b>CADC Model</b>	Low Risk (<10%)	234	13	0	5
	Intermediate Risk (10-90%)	55	364	0	13
	High Risk (≥90%)	0	0	0	0
<b>Outcome: Obstructive Disease</b>					
		<b>CADC Model with cardiac troponin</b>			
		Low Risk (<10%)	Intermediate Risk (10-90%)	High Risk (≥90%)	% Reclassified
<b>CADC Model</b>	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]			

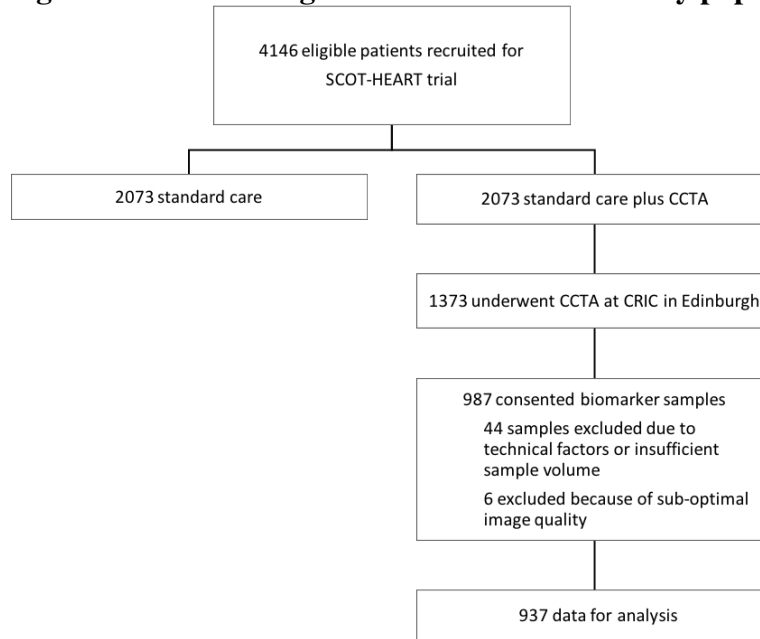
CADC, Coronary Artery Disease Consortium; NRI, net reclassification improvement; CI, confidence interval.

**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)

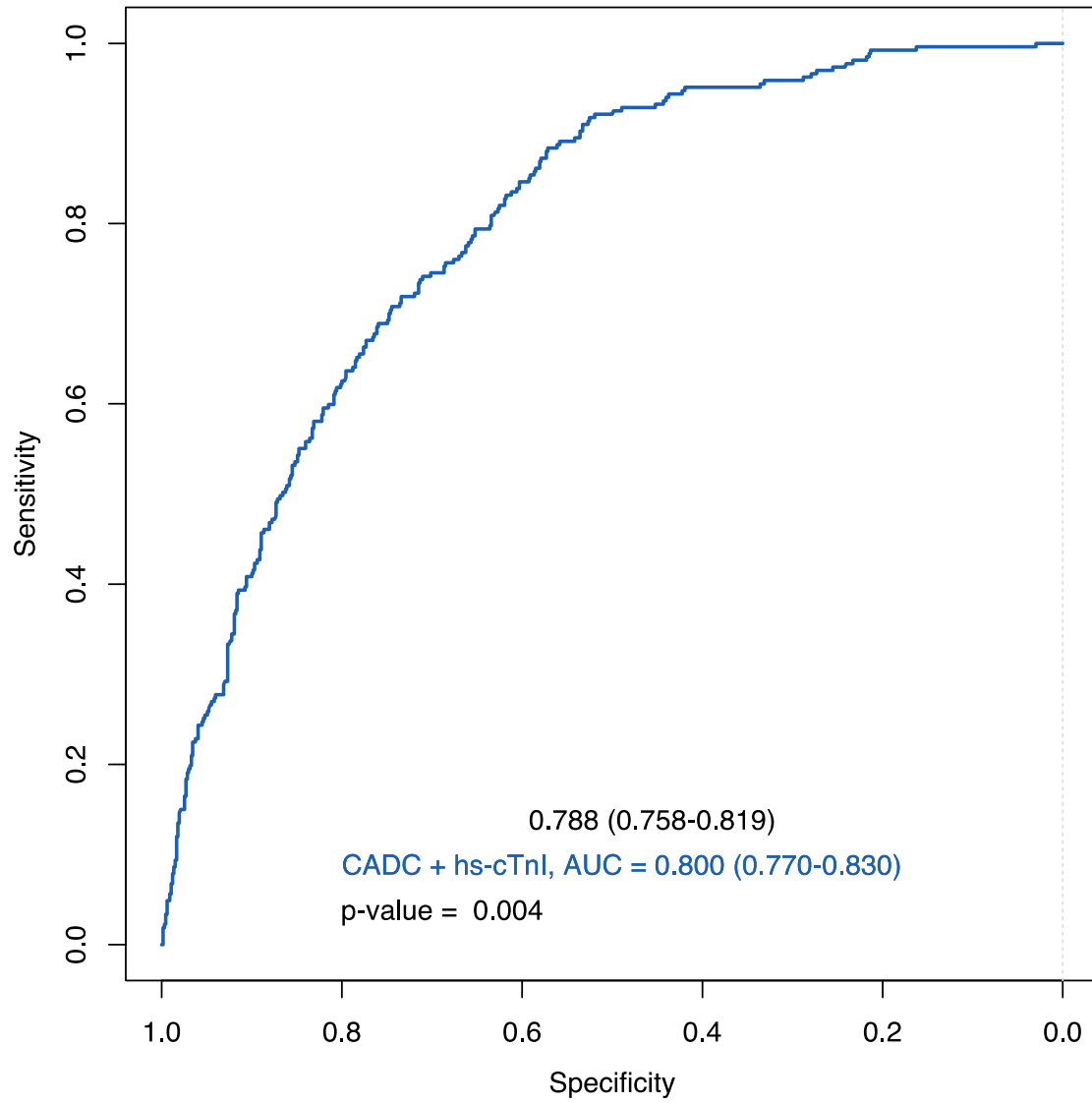
Data are mean (standard deviation), median [IQR], or value (%); CHD, coronary heart disease.

### Supplementary Figure 1. Consort diagram of biomarker substudy population



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

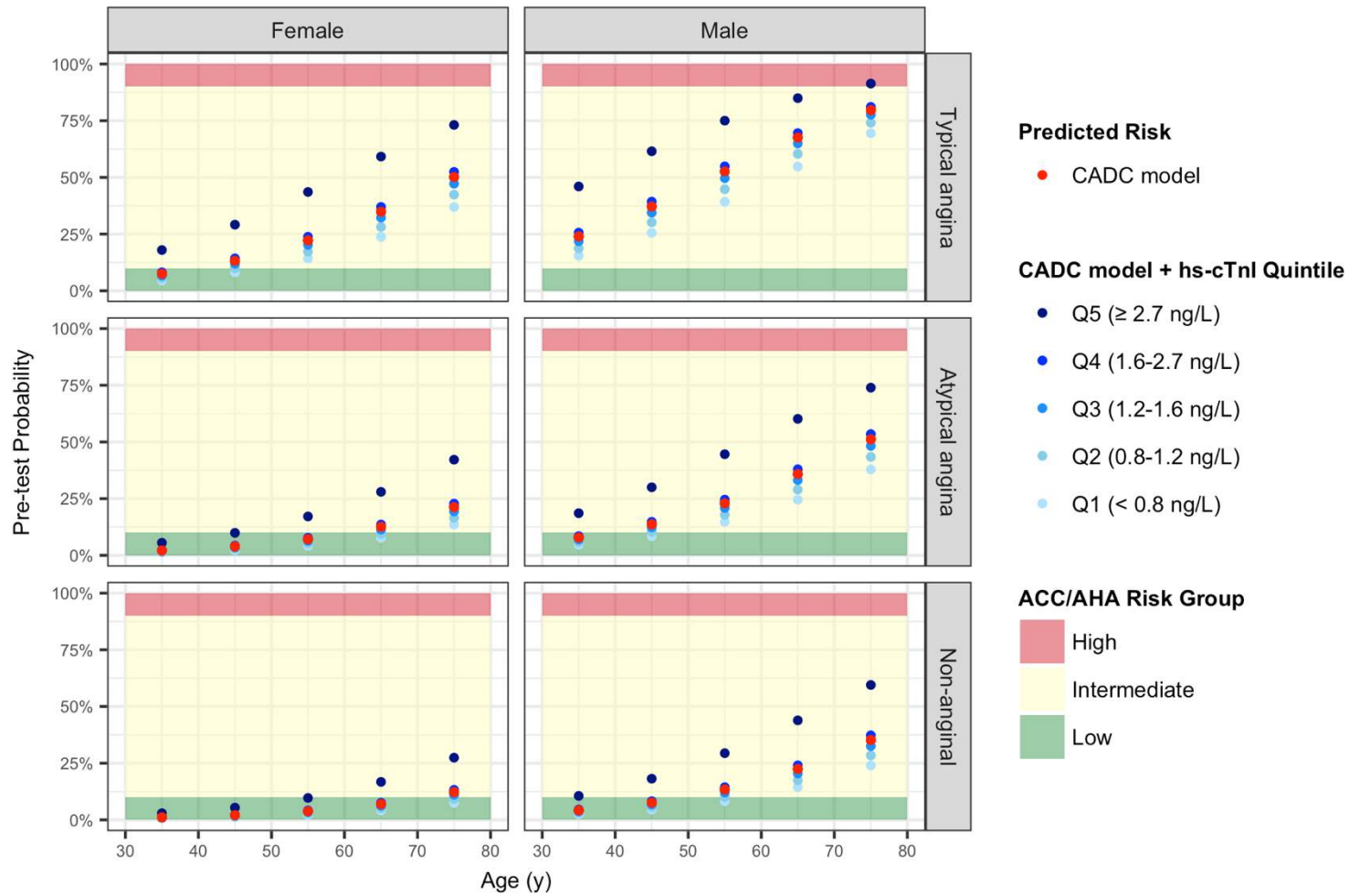
**Supplementary Figure 2. Receiver operating characteristic curve for the prediction of obstructive coronary artery disease**



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

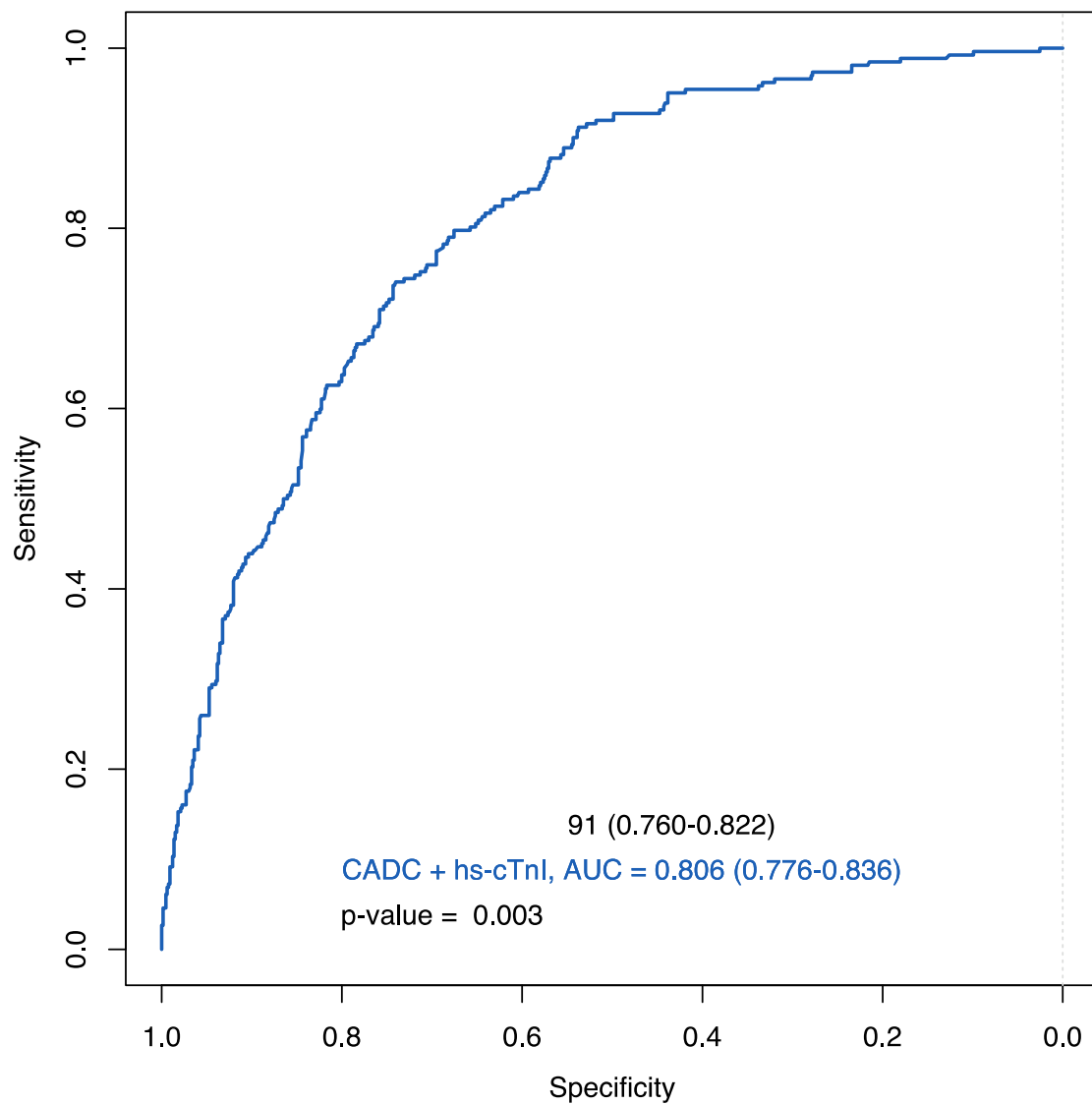
Supplementary Figure 3. Updated Risk Model for Obstructive CAD Incorporating Troponin Quintiles (Abbott hs-cTnI Assay)

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



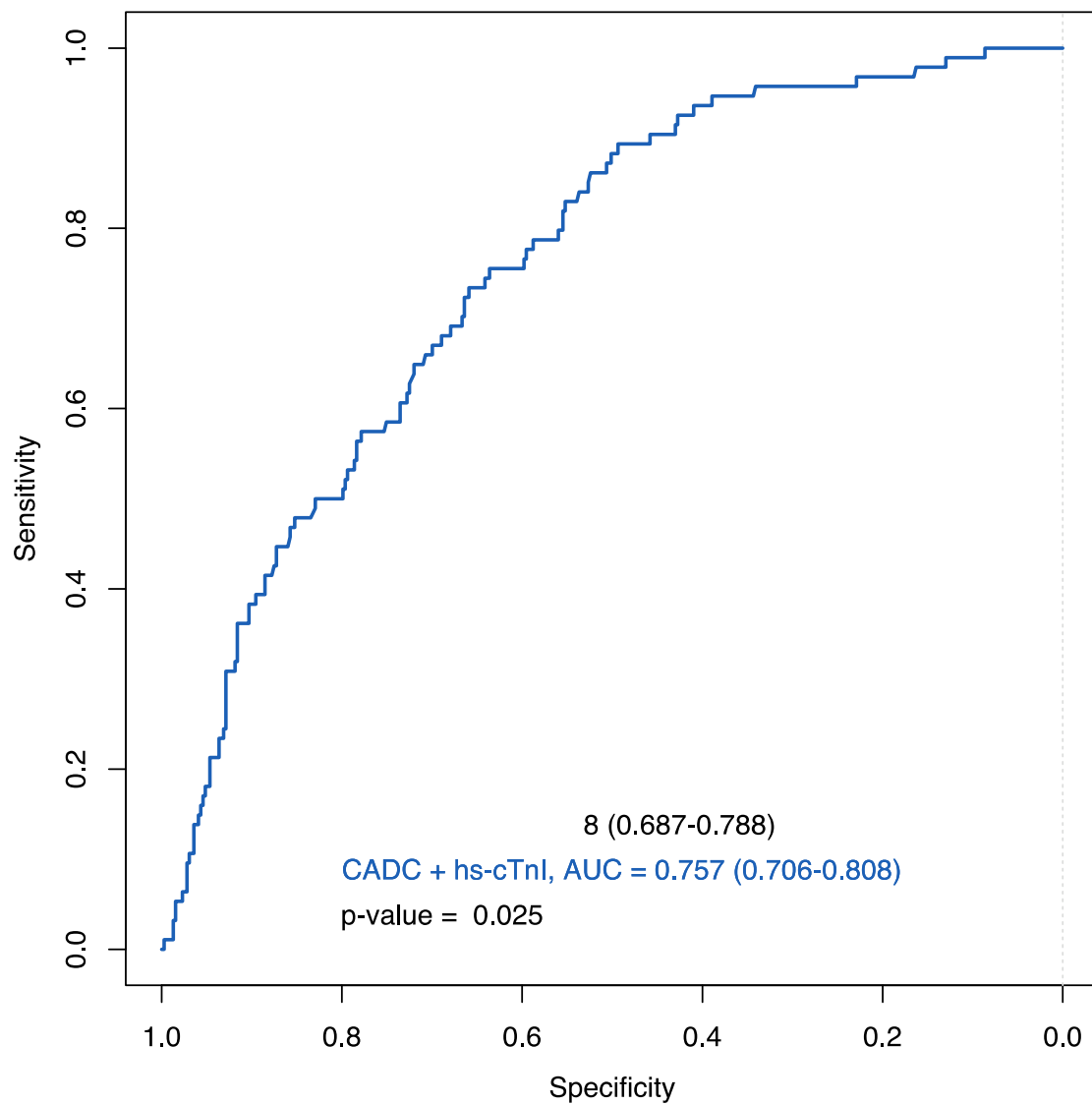


**Supplementary Figure 4. Receiver operating characteristic curve for the prediction of obstructive coronary artery disease (Abbott assay)**



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.