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

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Abstract

Background—We determined whether high-sensitivity cardiac troponin I can improve the estimation of the pre-test probability for obstructive coronary artery disease in patients with suspected stable angina.

Methods and Results—In a pre-specified sub-study of the Scottish COmputed Tomography of the Heart (SCOT-HEART) trial, 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 tomography angiography. Rates of obstructive coronary artery disease were compared with the pre-test probability determined by the Coronary Artery Disease Consortium (CADC) 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

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Disclosures
Singulex provided reagent, calibrators and controls without charge and undertook the analysis of cardiac troponin I. NLM has acted as a consultant for Abbott Laboratories, Beckman-Coulter, Roche and Singulex. All other authors have no conflicts of interest.

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coronary artery disease with a 5-fold increase across quintiles (9 to 48%, p<0.001) independent of known cardiovascular risk factors (odds ratio [OR] 1.35 [95% confidence interval (CI) 1.25-1.46] per doubling of troponin). Cardiac troponin concentrations improved the discrimination and calibration of the CADC model for identifying obstructive coronary artery disease (c-statistic 0.788 to 0.800, p=0.004; χ^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 pre-test probability risk categories (net reclassification improvement 0.062 [95% CI, 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 coronary artery disease in patients with suspected stable angina. Use of this test may improve the selection of patients for further investigation and treatment.

Clinical Trial Registration—Clinicaltrials.gov; Unique identifier NCT: 01149590

Keywords

cardiac troponin; high-sensitivity assays; stable angina; coronary artery disease; coronary computed tomography angiography

Journal Subject Terms

Biomarkers; Computerized Tomography; Chronic Ischemic Heart Disease; Clinical Studies

Introduction

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 suffer coronary death or non-fatal acute coronary syndrome in the 3 years following a diagnosis of stable angina (1). Importantly, this risk remains substantial even in those patients with symptoms deemed non-cardiac 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 (2). A number of national and international bodies have proposed standardised pathways that employ risk models to estimate the pre-test probability (PTP) of obstructive coronary artery disease and guide decision-making with regards to appropriate use of investigations (3–5). However, there is evidence both that these models may over-estimate risk (6–8) and that clinician use of stratification tools remains sub-optimal (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 coronary artery

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disease. 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 if routine quantification of plasma high sensitivity cardiac troponin I concentrations could improve estimation of the pre-test probability of obstructive coronary artery disease 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 upon reasonable request to the corresponding author.

Study design

The Scottish COmputed Tomography of the Heart (SCOT-HEART) trial was a prospective, multi-centre, randomised controlled study that investigated the role of coronary computed tomography angiography (CCTA) in patients referred to a specialist clinic with suspected angina due to 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 randomised to the intervention arm underwent CCTA imaging at one of 3 sites in addition to routine clinical assessment. There was a pre-specified biomarker sub-study which obtained blood samples from those participants where the CCTA was performed at the Clinical Research Imaging Centre in Edinburgh, UK. Recruitment began 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 prior to study participation.

High-sensitivity cardiac troponin I measurement

Venous blood samples for biomarker testing were obtained immediately prior to CCTA imaging. Blood was processed and stored at –80°C until analysed. Plasma high-sensitivity cardiac troponin I concentrations were measured using a high-sensitivity single molecule counting assay on the Erenna platform (Singulex Inc, Alameda, California, USA) which has a limit of detection (LoD) of 0.1 ng/L, a limit of quantification (LOQ, co-efficient of variation <10%) of 0.4 ng/L and a 99th centile upper reference limit (URL) 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 analysed using the ARCHITECT$_{STAT}$ high-sensitive troponin I assay (Abbott Laboratories, Abbott Park, Illinois, USA) 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 ng/L and 34 ng/L in women and men respectively (17, 18).

Coronary computed tomography angiography

Participants underwent coronary artery calcium scoring and CCTA using a 320-detector scanner (Aquilion One, Toshiba Medical Systems, Nasushiobara, Japan). Computed tomography images were analysed by 2 trained observers with excellent reproducibility (19). Differences in categorisation were resolved by consensus. Coronary artery calcium scoring was performed using dedicated software (VScore, Vital Images, Minnetonka, USA). Agatston score was calculated using a threshold of 130 HU (Hounsfield units) 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 one of five categories dependent on the degree of luminal cross-sectional area stenosis: normal (<10% stenosis), mild non-obstructive (10-49% stenosis), moderate non-obstructive (50-69% stenosis), obstructive (70-99% stenosis) or total/sub-total occlusion (100% stenosis). For the purposes of the primary outcome, obstructive coronary artery disease was defined prior to 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 one major epicardial vessel or ≥50% in the left main stem (14). Using previously described methods (20), the segment stenosis score (SSS) was quantified as a measure of overall atherosclerotic burden. All image analysis was performed blinded to the biomarker results.

The Coronary Artery Disease Consortium (CADC) model

The CADC is part of the European network for the Assessment of Imaging in Medicine (EuroAIM). In 2011 and 2012 the CADC updated and extended the earlier Diamond-Forrester model to estimate more accurately the pre-test probability (PTP) of obstructive coronary artery disease 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 coronary artery disease (3). Furthermore, it has recently been shown to provide more accurate estimates of the probability of obstructive coronary artery disease than the modified Diamond-Forrester model currently endorsed by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines and appropriate use criteria for the diagnosis of stable CAD (22–24). The ACC/AHA guideline uses two thresholds in order to stratify patients into three risk groups. Patients with a PTP less than 10% are deemed low-risk, those with a PTP between 10% and 90% are classed as intermediate risk, whilst those with a PTP ≥90% are high risk for CAD. It is widely recognised that the diagnostic utility of non-invasive testing is greatest in patients with intermediate pre-test probability 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 revascularisation.

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 angiography 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-squared and ANOVA tests being used to compare categorical and continuous variables, respectively. In logistic regression models, the probability of each patient having obstructive coronary artery disease was estimated. Cardiac troponin concentration and coronary artery calcium scores were log-transformed as linearising transformations. Associations were estimated unadjusted, and after adjusting for age, sex, chest pain characteristics, cardiovascular risk factors and non-invasive 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 (H-L) 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 ACC/AHA-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 to the existing CADC model in an independent cohort. Neither the intercept nor the coefficients were re-estimated for either model.

Results

Data collection and study population

The study population of the SCOT-HEART trial has previously been described (15). Between November 18th 2010 and September 24th 2014, 4,146 participants were recruited of whom 2,073 were randomly assigned to standard care plus CCTA and 1,778 of these underwent CCTA at one of three sites. Blood samples were obtained from 987 participants at the time of CCTA imaging at a single centre and 943 had plasma cardiac troponin I concentrations measured. CCTA image quality was non-diagnostic in 6 cases resulting in an analysis set comprising 937 participants (Supplementary Figure 1). The baseline characteristics were similar between trial participants with and without estimations of troponin concentrations (Supplementary Table 1).

Coronary computed tomography angiography

The median interval between randomisation and CCTA was 13 days (interquartile range [IQR] 7 to 18 days). The median coronary artery calcium score was 31 (IQR 0 to 281) Agatston Units (AU). CCTA demonstrated normal coronary arteries in 322 (34%), mild to

moderate non-obstructive disease in 348 (37%), and obstructive disease in 267 (28%) participants.

High-sensitivity cardiac troponin I concentrations

Using the Singulex assay, cardiac troponin I concentrations were above the LoD in 934/937 (99.6%) patients. The three 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 to 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 URL (10.9 ng/L) respectively. The median concentration of hs-cTnI in patients with obstructive coronary disease was 1.9 (IQR 1.3 to 3.1) ng/L whilst the median concentration of hs-cTnI in those without coronary obstruction was 1.2 (IQR 0.8 to 1.9) ng/L, p<0.001.

Higher cardiac troponin quintiles were associated with increasing age, male sex and a number of cardiovascular risk factors (Table 1). The majority (82.3%) of patients underwent exercise electrocardiography and this test was more likely to demonstrated inducible ischaemia 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 five-fold increase between the first and fifth quintiles (9.3% to 47.5%; Table 2). Each 2-fold increment in troponin concentration was associated with a 1.71-fold increment (95% confidence intervals (CI), 1.60-1.83) in the odds of identifying obstructive coronary artery disease on CCTA. This association was moderately attenuated after adjusting for age and sex (OR 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 (OR 1.27; 95% CI, 1.17-1.39; Supplementary Table 2).

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 a number of samples reported results below the LoD (200, 21.5%). Despite this, the overall findings were consistent with the primary analysis (Supplementary Tables 4-8, Supplementary Figures 2-3).

Update and extension of the CADC model

Compared to 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 (Supplementary Table 3). Goodness-of-fit for the baseline CADC model was inadequate (χ^2 = 20.2, HL p = 0.0095), although improved following re-estimation of the model intercept (difference in deviance 7.1, 1 degrees of freedom, p=0.0076). Adding cardiac troponin concentrations, further improved model fit (difference in deviance 16.3, 1 degrees of freedom, p<0.0001).

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The addition of cardiac troponin concentration improved overall model performance (D 0.230 to 0.257; Table 3) including discrimination (c-statistic: 0.788 to 0.800, p=0.0039; Supplementary Figure 4). The addition of cardiac troponin concentration also improved classification of patients into ACC/AHA 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 pre-test probability of CAD on the original CADC model (net reclassification index (NRI), 0.062 [95% CI, 0.035-0.089]).

External Validation

The validation cohort has been previously described (25, 26) and a summary of baseline characteristics is provided in Supplementary Table 8. The overall prevalence of obstructive coronary disease was 19.3% and again, a five-fold increase was seen across troponin quintiles. The addition of cardiac troponin concentration improved overall model performance (D 0.071 to 0.121) including discrimination (c-statistic: 0.738 to 0.757, p=0.025; Supplementary Figure 5), and model calibration (CADC model: $\chi^2 = 38.4$, HL $p < 0.0001$; CADC model including troponin: $\chi^2 = 13.0$, HL $p = 0.1123$) (Figure 2).

Discussion

In the assessment of suspected stable angina, measurement of high-sensitivity cardiac troponin I improves the accuracy of the pre-test probability of obstructive coronary artery disease as estimated using the existing guideline-endorsed CAD Consortium risk model. Applied in this manner, high-sensitivity troponin testing can appropriately reclassify one 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 pre-test probability for coronary disease (available at https://scotheart-mobile.herokuapp.com/)

Our study has a number of notable strengths. First, we chose to use a troponin assay with exceptional analytical 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, as this study was nested within a larger randomised trial of CCTA imaging in patients with suspected angina, we were able to minimise 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 coronary

artery disease in all patients. Fourth, the prospective nature of this study enabled detailed and accurate phenotypic characterisation of patients at baseline and comprehensive clinical follow-up. Finally, we demonstrated the externally 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 ischaemia and improve risk prediction. They also encourage analysis of lipid profiles and glycaemic indices as these represent important cardiovascular risk factors. Whilst 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 regarding several cardiovascular disorders including heart failure and myocardial infarction, and may even be a useful indicator of therapeutic response (12, 30–32).

Overall, our findings expand on this research demonstrating that troponin concentrations predict the presence of obstructive coronary artery disease in patients with suspected stable angina. The mechanisms behind this association, including ventricular strain (33), and myocardial ischaemia (34) 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, non-genetic (35) circulating biomarker has been shown to provide improved discrimination for the diagnosis of stable obstructive coronary artery disease 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 analytical characteristics but is presently available for research use only. We were able to measure troponin concentrations in more than 99% of the population across both sexes and a wide range of ages. Our 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 as 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 coronary computed tomography angiography. Although some authors may suggest that invasive coronary angiography remains the reference standard, it seems unlikely that troponin would be related to CT-defined coronary artery disease independent of the presence and extent of true coronary artery disease. As such, any misclassification is

likely to be non-differential with respect to troponin, and hence to cause us to underestimate the association between troponin and stable coronary artery disease, 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 non-invasively determined myocardial ischaemia (36). 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 (37). We also contend that a particular strength of this study arises from it being nested within a larger trial which randomised patients to coronary imaging, thereby minimising the case ascertainment bias inherent in earlier trials that only included patients referred for invasive coronary angiography. This applicability to the general 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 high-sensitivity cardiac troponin I concentrations independently predict the presence of obstructive coronary disease in patients with suspected stable angina. Employing this test within the chest pain clinic may improve the selection of patients for further investigation and treatment of coronary artery disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 non-invasive cardiac imaging tests to exclude this diagnosis

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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.

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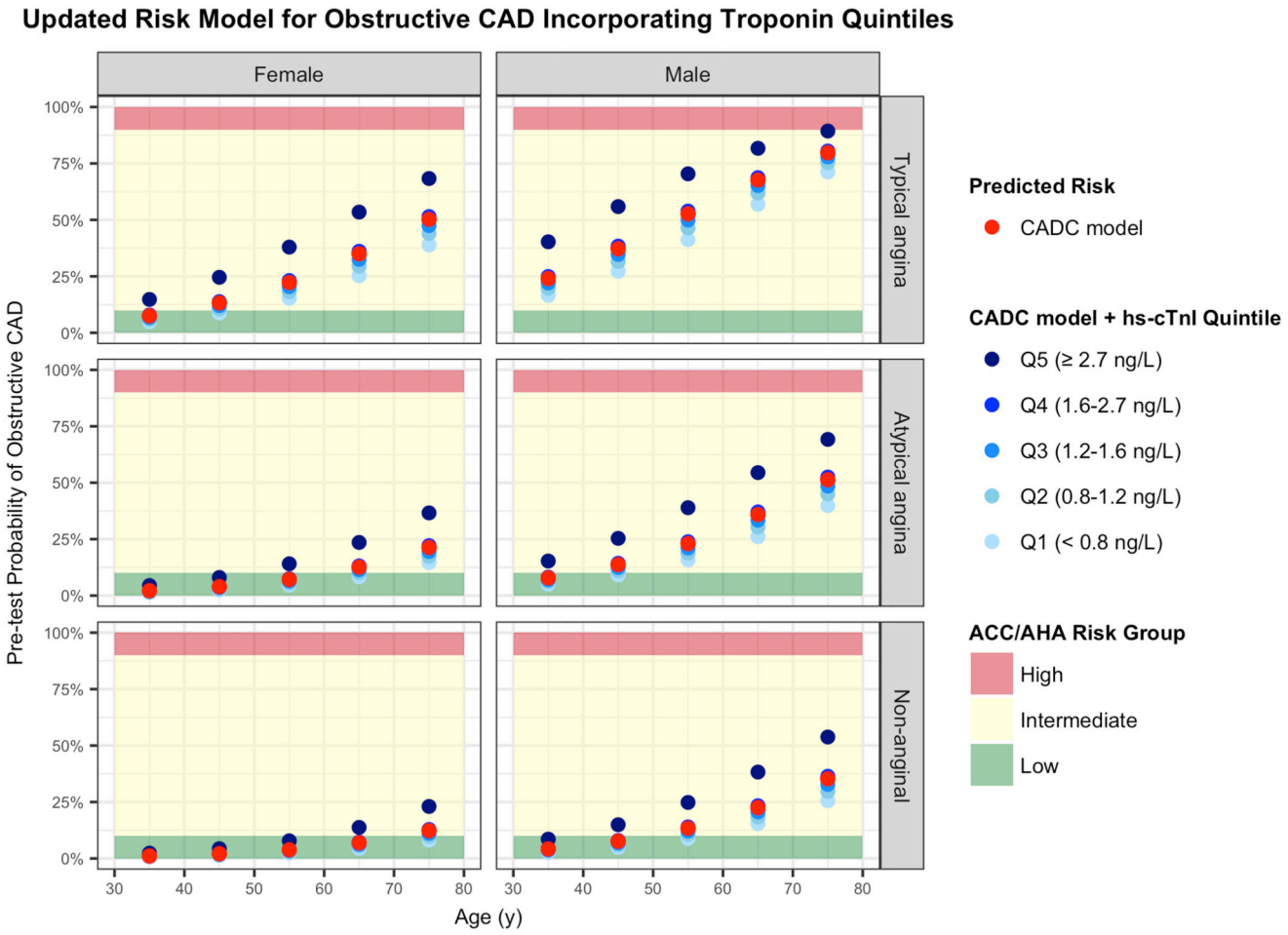

Figure 1. Cardiac troponin improves predicted risk of obstructive coronary artery disease in patients with suspected angina

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 ACC/AHA guidelines on the management of stable CAD. CAD, coronary artery disease; ACC, American College of Cardiology; AHA, American Heart Association; hs-cTnI, high-sensitivity cardiac troponin I; ECG, electrocardiography; y, years.

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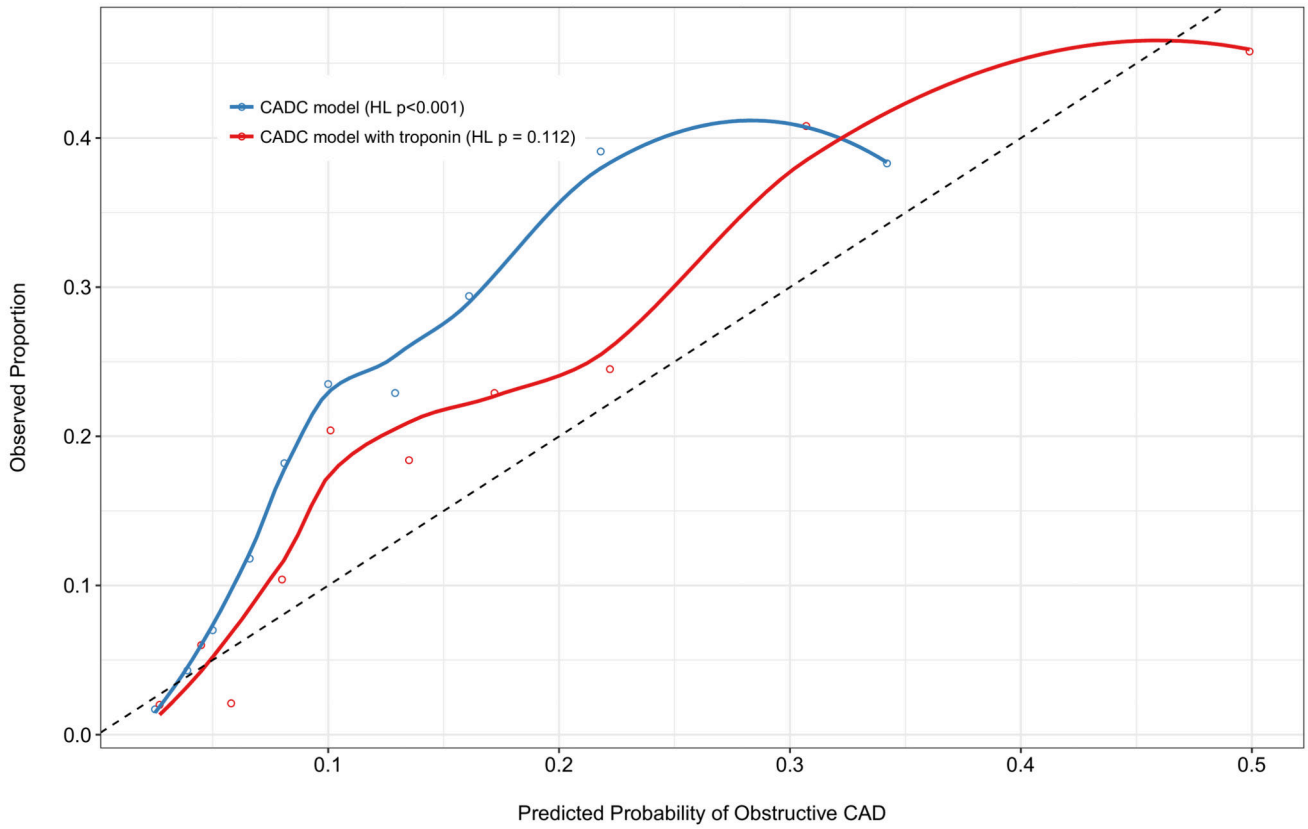

Figure 2. Model calibration within the external validation cohort

Plot demonstrates poor calibration of predicted probability vs observed proportion of obstructive coronary artery disease using the established CADC model (blue). Good model calibration is demonstrated within the validation cohort following the addition of troponin to the CADC model (red). The dashed line represents perfect calibration.

CADC, Coronary Artery Disease Consortium; HL, Hosmer-Lemeshow.

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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, years	51.8 (9.4)	57.0 (8.3)	59.0 (9.5)	60.7 (8.8)	60.7 (8.8)
Male, %	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)
Non-anginal	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)
Pre-existing 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-year 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 (standard deviation), median [IQR], or value (%); BMI, body mass index; CHD, coronary heart disease.

*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 (29)(see http://assign-score.com/)

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Table 2

Exercise electrocardiography and coronary computed tomography findings by troponin quintile

	Cardiac troponin I concentrations by quintile (ng/L)					
	Q1 (≤0.82)	**Q2 (0.83-1.16)**	**Q3 (1.17-1.61)**	**Q4 (1.62-2.66)**	**Q5 (>2.66)**	**p-value**
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)	
Non-obstructive 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 Score	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 (%); ECG, electrocardiography; IQR, interquartile range; CHD, coronary heart disease; SSS, segment stenosis score.

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Table 3
Coronary Artery Disease Consortium (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-square	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, Coronary Artery Disease Consortium; CI, confidence interval; NRI, net reclassification improvement; PTP, pre-test probability; PPV, positive predictive value; NPV, negative predictive value;

*both models apply updated intercept determined from SCOT-HEART population

†p = 0.0039 that true difference in AUC is not equal to 0.

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