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ORIGINAL RESEARCH

Cardiac Troponins and Cardiovascular Disease Risk Prediction

An Individual-Participant-Data Meta-Analysis

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ABSTRACT

BACKGROUND The extent to which high-sensitivity cardiac troponin can predict cardiovascular disease (CVD) is uncertain.

OBJECTIVES We aimed to quantify the potential advantage of adding information on cardiac troponins to conventional risk factors in the prevention of CVD.

METHODS We meta-analyzed individual-participant data from 15 cohorts, comprising 62,150 participants without prior CVD. We calculated HRs, measures of risk discrimination, and reclassification after adding cardiac troponin T (cTnT) or I (cTnI) to conventional risk factors. The primary outcome was first-onset CVD (ie, coronary heart disease or stroke). We then modeled the implications of initiating statin therapy using incidence rates from 2.1 million individuals from the United Kingdom.

RESULTS Among participants with cTnT or cTnI measurements, 8,133 and 3,749 incident CVD events occurred during a median follow-up of 11.8 and 9.8 years, respectively. HRs for CVD per 1-SD higher concentration were 1.31 (95% CI: 1.25-1.37) for cTnT and 1.26 (95% CI: 1.19-1.33) for cTnI. Addition of cTnT or cTnI to conventional risk factors was associated with C-index increases of 0.015 (95% CI: 0.012-0.018) and 0.012 (95% CI: 0.009-0.015) and continuous net reclassification improvements of 6% and 5% in cases and 22% and 17% in noncases. One additional CVD event would be prevented for every 408 and 473 individuals screened based on statin therapy in those whose CVD risk is reclassified from intermediate to high risk after cTnT or cTnI measurement, respectively.

CONCLUSIONS Measurement of cardiac troponin results in a modest improvement in the prediction of first-onset CVD that may translate into population health benefits if used at scale. (JACC. 2025;85:1471-1484)
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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

CRP = C-reactive protein

cTnI = cardiac troponin I

cTnT = cardiac troponin T

CVD = cardiovascular disease

eGFR = estimated glomerular filtration rate

ESC = European Society of Cardiology

HDL-C = high-density lipoprotein cholesterol

NT-proBNP = N-terminal pro-B-type natriuretic peptide

Guidelines recommend measurement of cardiac troponins—structural proteins released into the circulation following myocardial injury—for the assessment of patients with suspected acute coronary syndrome, during which circulating troponins are significantly elevated.[1-5] However, because assays for cardiac troponins (including cardiac troponin T [cTnT] and troponin I [cTnI]) are now highly sensitive and specific, they can quantify even very low circulating concentrations among apparently healthy individuals.[6,7]

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A key strategy in the prevention of cardiovascular disease (CVD) is the use of risk prediction algorithms that integrate conventional risk factors to identify individuals who could benefit most from preventive interventions, such as statin therapy.[8-10] Current clinical guidelines also recommend incorporating additional biomarkers when an individual's risk level does not meet a clear decision threshold, providing opportunities for enhanced risk stratification.[9,10] However, the population health utility of cardiac injury biomarkers such as troponins in improving CVD risk prediction remains uncertain.[8] Previous studies have focused only on measures of risk discrimination and recalibration but lacked modeling of the clinical implications of initiating guideline-recommended interventions (eg, statin therapy).[6,7,11,12] This limitation has hindered the evaluation of the potential clinical benefits of routinely measuring cardiac troponins in apparently healthy individuals for the prevention of CVD.

To address these gaps, our study aimed to answer 2 key questions. First, what is the improvement in CVD risk prediction when cardiac troponins are added to risk factors used in conventional risk algorithms? We analyzed data from 62,150 participants in 15 prospective longitudinal general population cohorts to assess the value of adding cardiac troponins to several conventional risk factors. Second, what is the estimated population health impact of incorporating cardiac troponins into CVD risk assessment? Using data from 2.1 million individuals in the UK CPRD (Clinical Practice Research Datalink),[13] we modeled the potential clinical benefit of initiating statin therapy in accordance with current guidelines.[8-10] To contextualize our findings, we compared the incremental predictive gains afforded by cardiac troponins with those provided by C-reactive protein (CRP), a plasma biomarker recommended for risk prediction in some CVD primary prevention guidelines,[9,10] estimated glomerular filtration rate (eGFR), a biomarker of kidney function that estimates how well the kidneys filter waste and excess fluid from the

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blood,[14] and N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker of neurohormonal activation that could also serve as an adjunct in the prediction of first-onset CVD.[15]

METHODS

DATA SOURCES. To evaluate the role of cardiac troponins in the primary prevention of CVD, we established the CAPRICE (CArdiac troponin in the PReventIon of Cardiovascular Events) collaboration, an international consortium of longitudinal cohort studies including individuals without a history of CVD at baseline that agreed to share individual-participant data. Details of the initial search strategy and methods used to collect and harmonize data are detailed in Supplemental Text 1. Studies were eligible if they had: 1) assayed cTnT[6,16-26] or cTnI[21,22,25,27-29] using a high-sensitivity assay;[5,30] 2) recorded baseline information on age, sex, smoking status (current vs other [former and never]), history of diabetes, systolic blood pressure, total and high-density lipoprotein cholesterol concentration (henceforth, "conventional risk factors"); 3) included participants without a known history of CVD (ie, coronary heart disease [CHD], stroke, transient ischemic attack, peripheral vascular disease, or cardiovascular surgery) at entry into the study; and 4) recorded cause-specific deaths and major cardiovascular morbidity (nonfatal myocardial infarction or stroke) over at least 1 year of follow-up.

Contributing studies classified deaths according to the primary cause (or, in its absence, the underlying cause) based on International Classification of Diseases coding, revisions 8 to 10, to at least 3 digits, or according to study-specific classification systems. We based ascertainment of fatal outcomes on death certificates, supplemented in 10 cohorts by additional data, and of nonfatal outcomes on World Health Organization (or similar) criteria for myocardial infarction and for stroke (Supplemental Table 1). The Newcastle-Ottawa scale was used to assess the quality of the included cohorts (Supplemental Table 2).[31] This study followed the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) reporting guidelines (Supplemental Text 2).[32]

To estimate the potential for disease prevention in a general population setting, we used data from the CPRD, a primary care database of anonymized medical records covering >20 million individuals opting into data linkage from more than 675 general practices in the United Kingdom.[13] Individual-level data from consenting practices in the CPRD have been linked to hospital episode statistics (HES) and the national death registry. Details of the CPRD data used and endpoint definition are provided in Supplemental Text 1. The present analysis involved records of 2.1 million patients, a random sample of all CPRD data, working under the assumption that individuals in this database should be broadly representative of the UK general population.

The study was conducted by the CAPRICE independent coordinating center at the University of Cambridge and the London School of Hygiene and Tropical Medicine. All cohorts were approved by the Institutional Review Boards of the participating institutions with participants providing written informed consent. The current study proposal was reviewed and approved by the Research Ethics Committee at the University of Cambridge.

DATA ANALYSIS. The analysis involved 4 interrelated components. First, we characterized cross-sectional associations of cardiac troponin concentrations with established and emerging risk factors. Second, we assessed associations of cardiac troponin concentrations with subsequent risk of first-onset CHD (defined as fatal or nonfatal myocardial infarction) and stroke, considering these outcomes alone and in combination. Third, we quantified the incremental value of information on cardiac troponin concentrations, beyond that of conventional risk factors, for predicting major CVD outcomes. Fourth, we assessed the population health relevance of adding cardiac troponins to conventional risk factors, by generalizing our analyses to the context of a UK population eligible for CVD risk assessment.

The primary outcome was a first-onset CVD event defined as the composite of any fatal or nonfatal CHD or any stroke.[33] Secondary outcomes included CHD and stroke separately. Participants contributed only the first CVD outcome (whether nonfatal or fatal) recorded during follow-up (ie, we did not include deaths preceded by nonfatal CVD events). We censored outcomes if a participant was lost to follow-up, died from causes other than CVD, or reached the end of the follow-up period. Individuals with cTnT or cTnI values at or below the limit of detection (3.00 ng/L for cTnT or 1.20 ng/L for cTnI) were assigned a value of 2.99 ng/L for cTnT or 1.19 ng/L for cTnI.[21,22] All continuous analyses were based on log-transformed cTnT and cTnI concentrations.

Cross-sectional correlates were estimated using linear fixed-effects regression of cTnT and cTnI on quintiles of continuous variables and categorical variables adjusted for age and sex.[34] To evaluate associations between cTnT and cTnI with primary and

TABLE 1 Baseline Characteristics of Participants From Cohorts With Measured Cardiac Troponin T or Troponin I

	Participants With Assessment of Cardiac Troponin T	Participants With Assessment of Cardiac Troponin I
Baseline characteristics		
Participants	50,523	28,090
Cohorts	11	6
Age, y	61 ± 11	60 ± 12
Female	26,292 (52)	13,881 (49)
Cardiovascular risk factors		
Current smoker	9,735 (19)	5,461 (20)
History of diabetes	4,154 (8)	1,317 (5)
Body mass index, kg/m^2	27.4 ± 5.0	26.9 ± 4.5
Systolic blood pressure, mm Hg	134 ± 22	139 ± 20
Total cholesterol, mmol/L	5.47 ± 1.09	5.76 ± 1.13
HDL cholesterol, mmol/L	1.41 ± 0.42	1.46 ± 0.42
Biomarkers of cardiac injury, inflammation, and renal function		
Cardiac troponin T, ng/L	5.0 (3.0-9.0)	-
Cardiac troponin I, ng/L	-	3.3 (2.1-5.2)
NT-proBNP, ng/mL	63 (33-121)	51 (26-94)
C-reactive protein, mg/L	1.89 (0.89-4.00)	1.50 (0.70-3.20)
Creatinine, μmol/l	81 (71-97)	81 (70-93)
Primary outcomes		
CVD cases	8,133	3,749
Follow-up, y	11.80 (8.67-17.74)	9.75 (8.25-12.42)

Values are n, mean ± SD, n (%), or median (Q1-Q3). Table shows information on all individuals, regardless of missing values in covariates included in subsequent regression models. Subsequent tables and figures are based on a complete-case analysis.

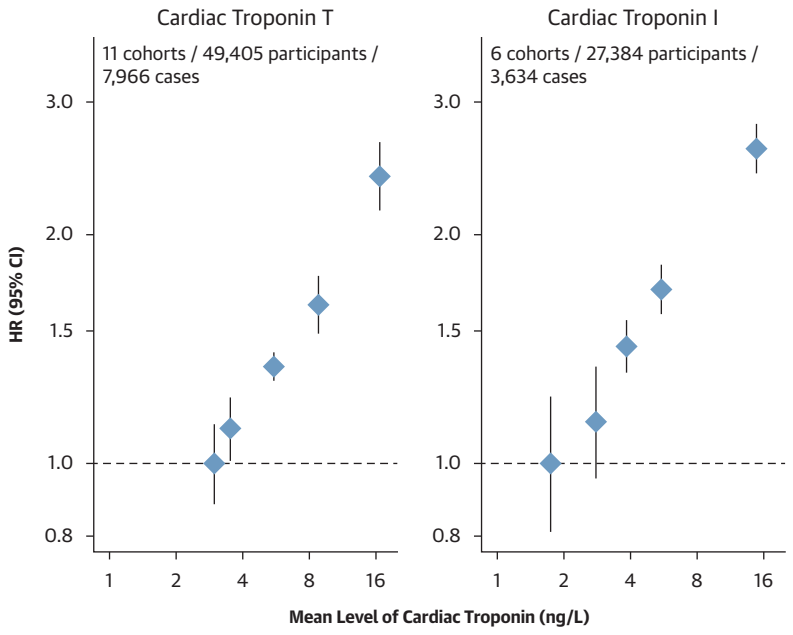
CVD = cardiovascular disease; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

secondary outcomes, HRs were calculated separately within each study using Cox proportional hazards regression models stratified by sex, using time-on-study as the timescale. The proportional hazards assumption was assessed using Schoenfeld residuals. HRs were adjusted for conventional risk factors (age, sex, smoking status, systolic blood pressure, history of diabetes, and total and high-density lipoprotein cholesterol [HDL-C] concentrations) and pooled across cohorts using multivariate random-effects meta-analysis.[35] We investigated effect modification by individual characteristics with formal tests of interaction.[35] To characterize shapes of associations, we calculated pooled HRs within overall fifths of cardiac troponin concentrations and plotted them against the pooled geometric mean of cardiac troponins concentration within each fifth. Additional analyses used martingale residuals, fractional polynomials, restricted maximum likelihood models, and Fine and Gray[36] competing risk-adjusted models.

We used CVD risk prediction models containing information about conventional risk factors first without and then with cardiac troponins. We quantified improvements in predictive ability using measures of risk discrimination and reclassification.[37,38] We calculated Harrell's C-indices and C-index changes within each study before pooling results weighted by the number of outcomes contributed. To avoid overestimation of the model's ability to predict risk, we applied a cross-validation approach (by leaving 1 cohort out).[39] We examined the change in C-index after adding cardiac troponins and other circulating biomarkers as both linear and quadratic terms. We calculated the continuous net reclassification improvement using data from studies in which both fatal and nonfatal CVD events had been recorded and separately among stroke and CHD cases and noncases.

To assess the population health relevance of adding cardiac troponins to conventional risk factors, we generalized our reclassification analyses to the context of a UK population eligible for CVD risk assessment (Supplemental Text 1). Using incidence rates calculated from CPRD data, we recalibrated the risk prediction models from our analysis to give 10-year risks that would be expected in a UK primary care setting, using methods previously described.[40] We modeled a population of 100,000 adults aged 40 to 89 years in CPRD, with an age and sex structure matching that of the UK general population, and CVD incidence rates observed among individuals without previous CVD or diabetes, and not taking statins.[41] We then modeled the population health impact of additional assessment of troponin for individuals at intermediate 10-year CVD risk based on conventional risk factors alone. The intermediate-risk group was defined according to the European Society of Cardiology (ESC) 2021 guidelines as a risk of 2.5% to <7.5% in those aged <50 years old, 5% to <10% in those aged 50 to <69 years old, and 7.5% to 15% in those aged 70 years or older.[8] We also modeled the potential population health impact for the intermediate-risk group defined by the National Institute for Health and Care Excellence guidelines.[41] Assuming a policy of statin allocation for people in the highest 10-year risk category, we estimated the potential that treatment allocation would result in a proportional reduction of ~20% in CVD risk across different individual-level characteristics.[42] Additional analyses assumed larger reductions in risk with statin treatment. The number needed to screen to prevent 1 CVD event was quantified from this modeling procedure and included 95% CIs calculated using 200 bootstrap standard errors. Findings are based on complete case analysis. Stata/SE version 17 was used for all analyses, with 2-sided *P* values and 95% CIs.

FIGURE 1 Associations of Cardiac Troponin T and Cardiac Troponin I With First-Onset Fatal or Nonfatal Cardiovascular Disease



HRs were adjusted for age, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) concentration (HDL-C concentration only for N-terminal pro-B-type natriuretic peptide concentration analysis) and models were stratified by sex. The first cardiac troponin group represents measurements at or below the limit of detection (LOD) and measurements higher than the LOD were grouped using quartiles of values. The cardiac troponin values were (natural) log-transformed and the x-axis was plotted on the log-scale and refers to the average levels of cardiac troponin calculated as the geometric mean. The size of the boxes is proportional to the inverse of the variance of the respective estimate. Error bars are 95% CIs, estimated from floated variances.

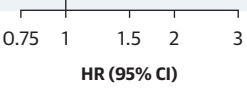
RESULTS

BASELINE CHARACTERISTICS AND ASSOCIATION WITH CVD OUTCOMES. Individual participant data were available on 62,150 participants without a history of CVD from 15 prospective studies. A total of 30,144 (48.5%) participants were women and the mean age was 61 ± 12 years. Most participants were enrolled in either Europe (65%) or North America (33%). cTnT was measured in 50,523 participants from 11 studies,[6,16-26] cTnI in 28,090 participants from 6 studies,[21,22,25,27-29] and 2 studies measured both.[21,25,43] Across all cohorts, cardiac troponin was measured using either the Elecsys Troponin T high-sensitive (Roche Diagnostics) or ARCHITECT$_{STAT}$ high-sensitivity troponin I (Abbott Diagnostics) assays.[44] Median concentrations were 5.0 ng/L (Q1-Q3: 3.0-9.0) and 3.3 ng/L (Q1-Q3: 2.1-5.2) for cTnT and cTnI, respectively. Details of the contributing studies are provided in **Table 1**, Supplemental Tables 3 and 4, and Supplemental Figure 1.[6,16-29] cTnT and cTnI concentrations increased with age and were lower in women, but were only weakly associated with several other characteristics, including history of diabetes, systolic and diastolic blood pressure, body mass index, total and HDL-C concentration, and creatinine (Supplemental Figures 2 to 4).

Among participants with an assessment of cTnT or cTnI, the median follow-up was 11.8 years (Q1-Q3: 8.7-17.7 years) and 9.8 years (Q1-Q3: 8.3-12.4 years), during which 8,133 and 3,749 incident CVD events occurred, respectively (**Table 1**, Supplemental Tables 3 and 4). cTnT and cTnI concentrations were approximately linearly associated with CVD risk (**Figure 1**, Supplemental Figure 5). HR for the composite CVD outcome (per 1 SD higher log-transformed concentration) adjusted for conventional risk factors were 1.31 (95% CI: 1.25-1.37) and 1.26 (95% CI: 1.19-1.33) for cTnT and cTnI, respectively (**Figure 2**, Supplemental Figures 6 and 7). Corresponding HRs for NT-proBNP, eGFR, and CRP for the composite CVD outcomes were 1.37 (95% CI: 1.30-1.44), 1.12 (95% CI: 1.02-1.22), and 1.16 (95% CI: 1.12-1.20), respectively (**Figure 2**, Supplemental Figures 8 and 9). HRs were similar for CHD and stroke outcomes, but slightly higher for fatal CVD outcomes (**Figure 3**). HRs were somewhat higher

FIGURE 2 Adjusted HRs of Conventional Cardiovascular Risk Factors and Biomarkers for Comparison With Cardiac Troponin T and Cardiac Troponin I

	Cohorts/Participants/Events	HR (95% CI)	*P* Value
Conventional Risk Factors			
Age, Per 5 Years	15/60,915/9,906	1.49 (1.40-1.58)	<0.001
Current Smoker	15/60,916/9,907	1.59 (1.43-1.77)	<0.001
History of Diabetes	15/60,916/9,907	1.67 (1.48-1.88)	<0.001
Systolic Blood Pressure, mm Hg	15/60,914/9,906	1.29 (1.22-1.36)	<0.001
Total Cholesterol, mmol/L	15/60,915/9,906	1.10 (1.06-1.15)	<0.001
High-Density Lipoprotein Cholesterol, mmol/L	15/60,915/9,906	1.15 (1.10-1.19)	<0.001
Circulating Cardiac-Related Biomarkers			
C-Reactive Protein, mg/L	13/39,825/7,037	1.16 (1.12-1.20)	<0.001
N-Terminal Pro B-Type Natriuretic Peptide, pg/mL	10/31,838/3,948	1.37 (1.30-1.44)	<0.001
eGFR, mL/min/1.73 m^2	9/27,184/3,869	1.12 (1.02-1.22)	0.012
Troponin-T, ng/L	11/49,405/7,966	1.31 (1.25-1.37)	<0.001
Troponin-I, ng/L	6/27,384/3,634	1.26 (1.19-1.33)	<0.001



HRs were estimated using Cox regression, stratified by cohort and sex, and adjusted for age at baseline, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol levels, where appropriate. For categorical variables, HRs are shown for patients with diabetes vs without, and for current smokers vs others. For continuous variables, HRs are shown per SD higher of each predictor to facilitate comparison, except age. For high-density lipoprotein cholesterol and estimated glomerular filtration rate (eGFR), the HR is shown per SD lower. The SD for the continuous variables are systolic blood pressure = 21.6, total cholesterol = 1.11, high-density lipoprotein = 0.42, natural log (ln) of C-reactive protein = 1.18, ln of N-terminal pro-B-type natriuretic peptide = 1.13, ln of cardiac troponin T = 0.68, ln of cardiac troponin I = 0.85, and eGFR = 16.2.

for female compared with male individuals but did not vary substantially with levels of other conventional risk factors or in other clinically relevant subgroups (Supplemental Figures 10 and 11). Similar results were found using competing risk-adjusted models and meta-analysis using restricted maximum likelihood method (Supplemental Figures 12 and 13).

INCREMENTAL VALUE IN RISK PREDICTION. We assessed the incremental predictive ability of cardiac troponins using measures of risk discrimination and reclassification, adding cTnT or cTnI to models containing conventional CVD risk factors. For incident CVD, the C-index increased by 0.015 (95% CI: 0.012-0.018), from 0.673 (95% CI: 0.667-0.679) to 0.688 (95% CI: 0.682-0.691) for cTnT, and by 0.012 (95% CI: 0.009-0.015), from 0.715 (95% CI: 0.706-0.723) to 0.727 (95% CI: 0.718-0.735) for cTnI (**Figure 4**). Similar results were observed using cross-validation analyses (Supplemental Figure 14). Continuous net reclassification index values were 6% (95% CI: 3%-9%) among CVD cases and 22% (95% CI: 20%-23%) among noncases for cTnT, and 5% (95% CI: 2%-9%) among CVD cases and 17% (95% CI: 15%-18%) among noncases for cTnI (**Table 2**, Supplemental Figure 15). Supplemental Table 5 shows the continuous net reclassification index among stroke and CHD cases and noncases.

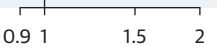
Incremental risk prediction demonstrated by cardiac troponins was similar to that of NT-proBNP but greater than CRP and eGFR (**Figure 4**, Supplemental Figures 16 and 17). The addition of cardiac troponins to CRP demonstrated incremental risk discrimination when compared to adding cardiac troponin alone. In contrast, the addition of cardiac troponins to NT-proBNP or eGFR did not substantially improve risk discrimination, with overlapping CIs. Improvements in C-index with information on cardiac troponin concentrations were possibly greater among older individuals and people with a history of diabetes (Supplemental Figures 18 and 19). Models including cardiac troponins showed good calibration, with good agreement between the observed and predicted CVD risks (Supplemental Figure 20).

ESTIMATE FOR THE POTENTIAL OF DISEASE PREVENTION. For cTnT, and using a conventional cardiovascular risk factor model alone, 35,675 (36%) of 100,000 individuals would be classified as having intermediate 10-year risk according to the 2021 ESC Prevention Guidelines who were not already taking or

FIGURE 3 **Associations of Cardiac Troponin T and Cardiac Troponin I Concentrations With Several Incident First-Onset Cardiovascular Outcomes**

Cardiac Troponin T

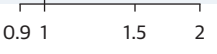
Outcome	Cohorts/Participants/Events	HR (95% CI)	*P* Value
Fatal or Nonfatal Cardiovascular Disease	11/49,405/7,966	1.31 (1.25-1.37)	<0.001
Coronary Heart Disease	11/49,405/4,045	1.32 (1.23-1.41)	<0.001
Fatal	10/47,688/1,104	1.49 (1.36-1.64)	<0.001
Nonfatal	11/49,405/2,932	1.26 (1.15-1.37)	<0.001
Stroke (Any Type)	11/49,405/2,988	1.21 (1.15-1.27)	<0.001
Ischemic	7/40,484/1,605	1.21 (1.13-1.30)	<0.001
Hemorrhagic	7/40,484/249	1.21 (1.02-1.44)	0.033
Unclassified	8/36,737/1,028	1.27 (1.10-1.46)	<0.001
Fatal Cardiovascular Disease	11/49,400/3,815	1.47 (1.37-1.57)	<0.001



HR (95% CI) Per SD Higher

Cardiac Troponin I

Outcome	Cohorts/Participants/Events	HR (95% CI)	*P* Value
Fatal or Nonfatal Cardiovascular Disease	6/27,384/3,634	1.26 (1.19-1.33)	<0.001
Coronary Heart Disease	6/27,384/1,604	1.22 (1.08-1.39)	0.002
Fatal	6/27,384/382	1.29 (1.03-1.62)	0.028
Nonfatal	6/27,384/1,222	1.22 (1.09-1.37)	<0.001
Stroke (Any Type)	6/27,384/1,452	1.22 (1.15-1.29)	<0.001
Ischemic	4/18,082/321	1.25 (1.06-1.47)	0.009
Hemorrhagic	5/23,915/103	1.15 (0.93-1.41)	0.189
Unclassified	5/26,545/962	1.21 (1.11-1.31)	<0.001
Fatal Cardiovascular Disease	6/27,384/1,781	1.36 (1.24-1.50)	<0.001



HR (95% CI) Per SD Higher

HRs adjusted for age, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol and stratified by sex and cohort. Cardiac troponin values were (natural) log-transformed (ln) and left as continuous values. HRs represent 1-SD higher ln cardiac troponin value. Error bars are 95% CIs and box sizes are unweighted. Individuals only needed at least 1 component outcome to be defined as a case for the composite outcome. The SD is 0.68 for ln of cardiac troponin T and 0.85 for ln of cardiac troponin I.

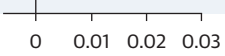
eligible for statin treatment (ie, people without a history of diabetes or CVD) (**Figure 5**). Assessment of cTnT in these individuals (ie, a "targeted" approach focusing only on people judged to be at intermediate 10-year risk of CVD after initial screening with conventional risk factors alone) would re-classify 2,754 intermediate-risk individuals as high risk, of whom approximately 437 (16%) would be expected to have a CVD event within 10 years. This would correspond to an increase of about 4.6% (437 of 9,487) of the CVD events already classified at high risk using conventional risk predictors alone.

Assuming statin allocation as per current ESC guidelines and statin treatment conferring a 20% relative risk reduction,[42,45] such targeted assessment of cTnT among the intermediate-risk group would help prevent 87 events over the next 10-year period, equating to the screening of 408 participants to prevent 1 event (**Central Illustration**). Similar findings were observed with the targeted assessment of cTnI, with 473 participants needing to be screened to prevent 1 event (**Figure 5**), and when analysis involved cutoffs for clinical risk categories defined by National Institute for Health and Care Excellence guidelines (Supplemental Table 6). For comparison, the numbers needed to screen to prevent 1 event with targeted assessment of NT-proBNP and CRP would be 468 and 593, respectively (Supplemental Table 7). Assuming a larger relative risk reduction from statin treatment of 30% or 40%,[46] the numbers needed to screen to

FIGURE 4 **Improvement in Risk Discrimination for First-Onset Fatal or Nonfatal Cardiovascular Disease by Addition of Information About Cardiac Troponin T and Cardiac Troponin I Concentration Compared With That About HDL-C and Total Cholesterol, CRP, or NT-proBNP Concentration**

Cardiac Troponin T

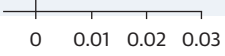
	C-Index (95% CI)	Δ C-Index (95% CI)
Lipids and Troponin Comparison	**11 Cohorts/49,405 Participants/7,966 Events**	
Conventional Risk Factors Without Lipids	0.6729 (0.6668-0.6790)	[Reference]
Plus HDL-C and total cholesterol	0.6775 (0.6714-0.6835)	0.0046 (0.0030-0.0061)***
Plus troponin	0.6880 (0.6820-0.6941)	0.0151 (0.0124-0.0178)***
Plus HDL-C, total cholesterol and troponin	0.6922 (0.6862-0.6982)	0.0193 (0.0164-0.0223)***
CRP and Troponin Comparison	**9 Cohorts/28,385 Participants/5,100 Events**	
Conventional Risk Factors With Lipids	0.6680 (0.6603-0.6758)	[Reference]
Plus troponin	0.6828 (0.6752-0.6904)	0.0148 (0.0113-0.0182)***
Plus CRP	0.6717 (0.6640-0.6794)	0.0037 (0.0018-0.0056)***
Plus CRP and troponin	0.6854 (0.6778-0.6930)	0.0174 (0.0137-0.0211)***
NT-proBNP and Troponin Comparison	**8 Cohorts/27,736 Participants/3,621 Events**	
Conventional Risk Factors With Lipids	0.6784 (0.6690-0.6877)	[Reference]
Plus troponin	0.6914 (0.6822-0.7006)	0.0130 (0.0088-0.0172)***
Plus NT-proBNP	0.6912 (0.6819-0.7006)	0.0129 (0.0079-0.0179)***
Plus NT-proBNP and troponin	0.6973 (0.6880-0.7066)	0.0190 (0.0134-0.0245)***



Change in C-Index (95% CI) vs Reference Model

Cardiac Troponin I

	C-Index (95% CI)	Δ C-Index (95% CI)
Lipids and Troponin Comparison	**6 Cohorts /27,384 Participants/3,634 Events**	
Conventional Risk Factors Without Lipids	0.7148 (0.7064-0.7233)	[Reference]
Plus HDL-C and total cholesterol	0.7186 (0.7102-0.7269)	0.0037 (0.0013-0.0062)**
Plus troponin	0.7265 (0.7181-0.7349)	0.0117 (0.0088-0.0145)***
Plus HDL-C, total cholesterol and troponin	0.7291 (0.7208-0.7374)	0.0143 (0.0108-0.0178)***
CRP and Troponin Comparison	**5 Cohorts/15,318 Participants/2,957 Events**	
Conventional Risk Factors With Lipids	0.7130 (0.7039-0.7221)	[Reference]
Plus troponin	0.7244 (0.7153-0.7334)	0.0114 (0.0084-0.0144)***
Plus CRP	0.7181 (0.7091-0.7272)	0.0052 (0.0024-0.0080)***
Plus CRP and troponin	0.7282 (0.7192-0.7371)	0.0152 (0.0113-0.0191)***
NT-proBNP and Troponin comparison	**3 Cohorts/15,535 Participants/969 Events**	
Conventional Risk Factors With Lipids	0.7240 (0.7069-0.7410)	[Reference]
Plus troponin	0.7321 (0.7152-0.7489)	0.0081 (0.0032-0.0130)**
Plus NT-proBNP	0.7296 (0.7125-0.7467)	0.0057 (−0.0006 to 0.0119)
Plus NT-proBNP and troponin	0.7348 (0.7179-0.7517)	0.0109 (0.0039-0.0178)



Change in C-Index (95% CI) vs Reference Model

Cardiac troponin, C-reactive protein (CRP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) values were all (natural) log-transformed. The change in C-index is in reference to the model that included information about age, smoking status, systolic blood pressure, history of diabetes, high-density lipoprotein cholesterol (HDL-C), and concentration of total cholesterol, where relevant. Note that the reference model has a higher C-index for the studies measuring cardiac troponin I compared with cardiac troponin T. $^{**}P < 0.01$, and $^{***}P < 0.001$.

TABLE 2 Continuous Net Reclassification Index and 95% CI for 10-year Fatal or Nonfatal Cardiovascular Disease (Generalized to a Primary Prevention Population)

Conventional risk factors plus cardiac troponin T	
No. of cohorts/participants/events	11/49,405/7,966
Noncases	22 (20-23)
Cases	6 (3-9)
Conventional risk factors plus cardiac troponin I	
No. of cohorts/participants/events	6/27,384/3,634
Noncases	17 (15-18)
Cases	5 (2-9)
Conventional risk factors plus CRP	
No. of cohorts/participants/events	14/39,826/7,037
Noncases	19 (17-20)
Cases	−2 (−5 to 1)
Conventional risk factors plus NT-proBNP	
No. of cohorts/participants/events	11/31,836/3,948
Noncases	21 (19-23)
Cases	−5 (−8 to 0)

Conventional risk factors included age at baseline, smoking status, history of diabetes, systolic blood pressure, total cholesterol, and high-density lipoprotein. Net reclassification index is expressed as a percentage. Cox models were performed by cohort and sex.

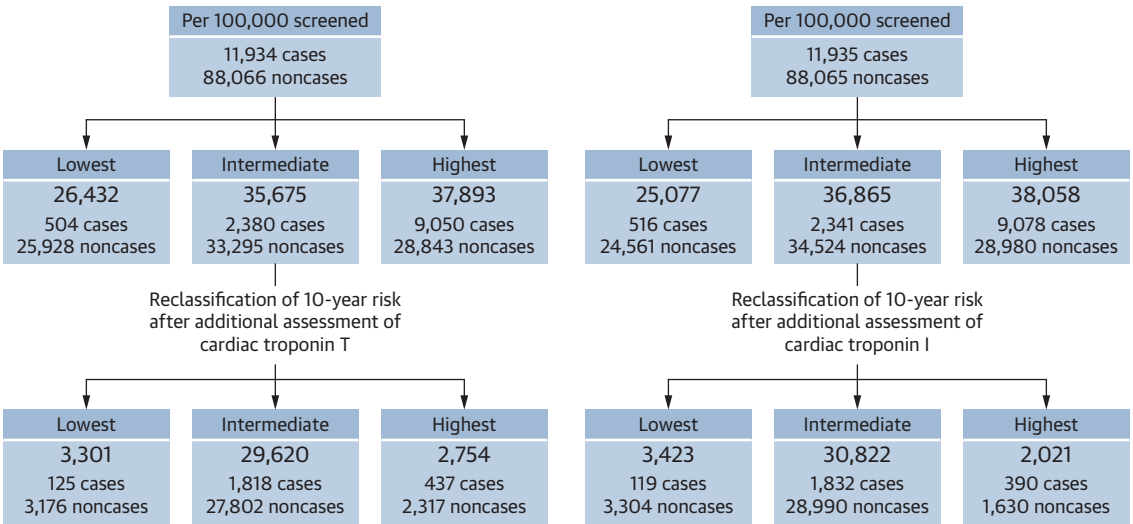
CRP = C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviation as in Table 1.

prevent 1 event with targeted assessment of cTnT or cTnI would be between 205 and 273 and 237 and 316, respectively (Supplemental Table 8).

DISCUSSION

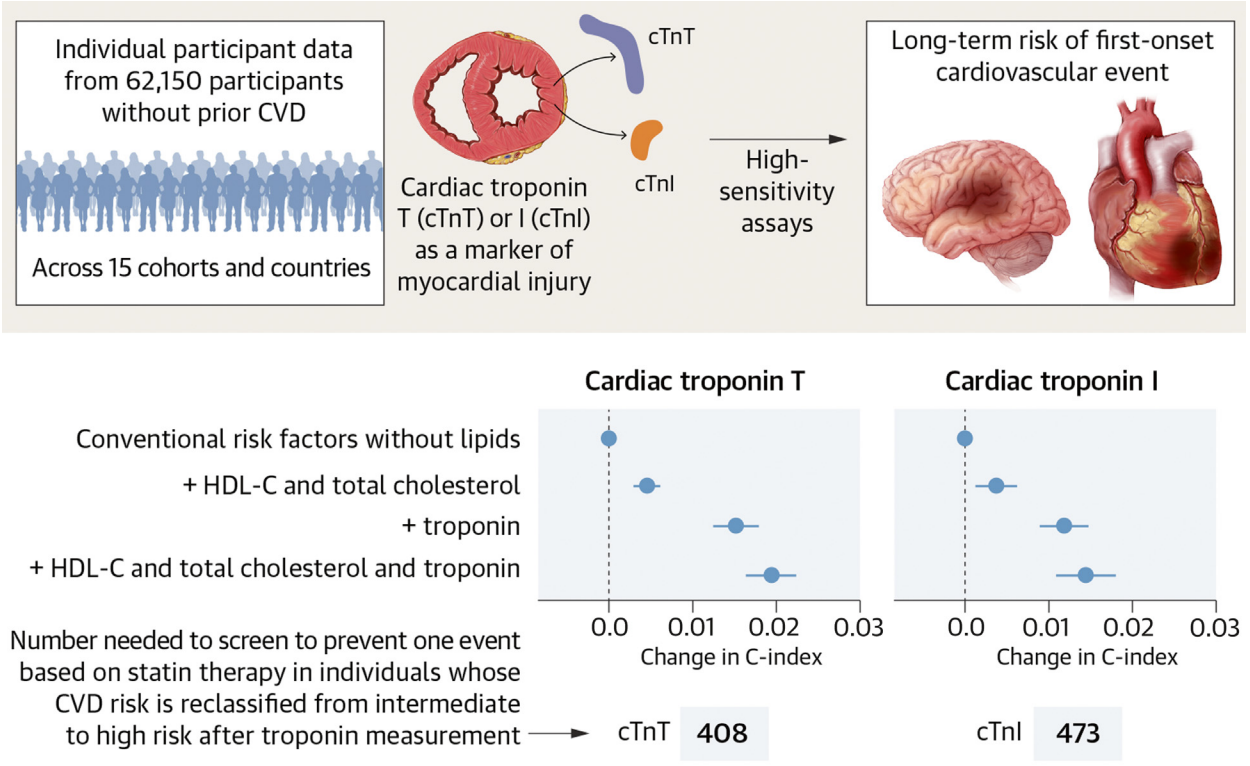
In an analysis comprising individual participant data on >60,000 participants from 15 prospective cohort studies, we studied the potential value of adding information on cardiac troponins to conventional cardiovascular risk factors used to predict first-onset CVD risk. We then modeled a scenario using CVD incidence rates derived from data from 2.1 million people from general practices in the United Kingdom, in which cardiac troponins were assessed in people considered to be at intermediate risk by current prevention guidelines after initial screening using conventional risk factors alone. Overall, our results suggest that the addition of cardiac troponins to conventional risk factors can provide a modest improvement in the prediction of first-onset CVD, which, if applied at scale, could help detect up to 5% more CVD events than the use of conventional risk

FIGURE 5 Estimated Population Health Impact With Targeted Assessment of Cardiac Troponin T or Cardiac Troponin I Among 100,000 UK Adults in a Primary Care Setting Using Thresholds From European Society of Cardiology 2021 Guidelines



Reclassification analyses was contextualized to a UK population eligible for cardiovascular disease screening that did not include people with a history of diabetes. Those with a history of diabetes were excluded from the calculations of screening benefit because people with diabetes are eligible for statin treatments irrespective of baseline risk. The conventional risk factors model included baseline age, smoking status, systolic blood pressure, total cholesterol, and high-density lipoprotein.

CENTRAL ILLUSTRATION **Cardiac Troponin in the Prevention of Cardiovascular Events (CAPRICE): A Collaborative Individual Patient Data Meta-Analysis**



Shah ASV, et al. JACC. 2025;85(14):1471–1484.

factors alone. Our results have potential implications for CVD risk prediction and for the evaluation of the population health utility of cardiac troponins.

First, our modeling suggests that, if applied to the standard UK general population aged 40 to 89 years, additional use of cardiac troponins could help detect and prevent more CVD events over the next 10 years beyond the assessment of conventional risk factors alone. In a modeled scenario in which cardiac troponins were assessed in a primary care setting among individuals considered at intermediate CVD risk after initial screening with conventional risk predictors alone, our data suggest 1 extra CVD outcome could be prevented over a period of 10 years for approximately every 400 people in whom cardiac troponins are assessed provided this is coupled with initiation of statin therapy in accordance with current guidelines.[8]

Second, to provide clinical context, we compared the incremental predictive gains afforded by information on cardiac troponins with those provided by CRP, eGFR, and NT-proBNP. Our results demonstrated that cardiac troponins provided a greater gain in predictive accuracy compared with CRP and eGFR, whereas NT-proBNP yielded similar results. Although cardiac troponins potentially offered additional improvements in risk discrimination beyond those provided by CRP—suggesting these biomarkers might capture distinct aspects of CVD risk—the improvements from cardiac troponins and NT-proBNP were not additive. This suggests that cardiac troponins and NT-proBNP provide somewhat overlapping information about myocardial damage in the context of primary prevention. We also found that improvements in risk discrimination with cardiac troponins were

greater than those provided by total cholesterol and HDL-C, even though our evaluation was skewed in favor of lipid measurements since we added total cholesterol and HDL-C only to other conventional risk factors (and omitted cardiac troponins), whereas we added cardiac troponins to all conventional risk factors, including total cholesterol and HDL-C. We restricted comparisons of cardiac troponins with other circulating biomarkers to participants who had complete information on these measurements, thereby avoiding potential bias.

Third, we found that cTnT and cTnI provide similar predictive information for CVD risk prediction, indicating that either biomarker can be effectively utilized in clinical settings for the assessment of first-onset CVD risk. This equivalence in predictive ability suggests that the choice between cTnT and cTnI can be flexible, depending on availability and specific clinical scenarios. Our findings align with previous studies that have demonstrated comparable diagnostic and prognostic capabilities of these biomarkers in various populations and clinical conditions.[3,7,47]

Fourth, our main model assumed that information on cardiac troponins would provide similar predictions of CVD risk across population subgroups. However, an exploratory analysis suggested that these biomarkers could provide more accurate risk prediction in older individuals and in those with a history of diabetes. These findings require cautious interpretation because they could arise, at least to some extent, due to the play of chance from the conduct of multiple statistical tests (because we explored interactions of cardiac troponins with several characteristics). Nevertheless, the potential for more accurate risk prediction in these subgroups raises the possibility that subclinical CVD may be more prevalent among these individuals,[48] warranting further investigation to determine whether targeting the assessment of cardiac troponins in older individuals and in those with diabetes enhances screening efficiency.

STUDY STRENGTHS AND LIMITATIONS. Our study had major strengths. In all cohorts, cardiac troponin concentrations were measured using commonly used diagnostic assays, with potential for clinical use. We recorded information about the incidence of various CVD outcomes using well-validated endpoint definitions. We centrally analyzed individual-participant data, which were harmonized from prospective studies with extended follow-up, enabling time-to-event analyses, exclusion of people with a baseline history of CVD, and adoption of a uniform approach to statistical analyses. Because of its considerable statistical power, we could provide precise estimates, even for analyses that involved categorization of cardiac troponin concentrations. To enhance validity further, we restricted analyses to people with complete information about a set of relevant risk factors. We used multiple complementary metrics of risk discrimination and reclassification, as well as different absolute risk thresholds used in different clinical guidelines. The broadly concordant results we observed across these metrics support the validity of our main conclusions. To extend the relevance of our findings to a primary care population, we also conducted modeling using the UK CPRD, adapting (recalibrating) our findings to be more representative of the general population. The generalizability of our findings was enhanced by the inclusion of data from 10 countries and by the robustness of results to various sensitivity analyses.

Our study had some potential limitations. We used a convenience sample of cohorts derived primarily from middle- to older-aged individuals of European continental ancestry, which may limit the generalizability of our findings to other populations. Only 2 contributing cohorts measured both cTnT and cTnI, preventing a reliable head-to-head comparison of cardiac troponins.[21,25,43] We used a conventional 10-year timeframe and standard clinical risk categories, acknowledging that reclassification analyses are intrinsically sensitive to choices of follow-up interval and clinical risk categories. A somewhat greater population health impact than suggested by our main analysis would be estimated if we had used less conservative modeling assumptions (eg, more effective statin regimens, additional CVD-lowering medications, for example antihypertensives, and longer time horizons). Conversely, our models could have overestimated the potential benefits of assessing cardiac troponins because not all people eligible for statins will receive them, be willing to take them, or adhere to treatment. In addition, if competing risks are not adequately accounted for, population health benefits could be overestimated.[36] Data were unavailable to assess the added value of incorporating cardiac troponin measurements into the risk prediction tools currently recommended by US and UK guidelines (ie, QRISK3[49] and PREVENT [Predicting Risk of cardiovascular disease EVENTs][50]), as well as when using additional risk modifiers such as coronary calcium scores or polygenic risk scores.[51] Finally, a comprehensive health economic evaluation or an analysis of the feasibility of widespread troponin screening were beyond the scope of the present study.

CONCLUSIONS

We conclude that measurement of cardiac troponin in addition to conventional risk factors results in a modest improvement in the prediction of first-onset CVD that may translate into population health benefits if used at scale.

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APPENDIX For supplemental text, figures, and tables, please see the online version of this paper.

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