Ultrasensitive Troponin I and Incident Cardiovascular Disease

Arteriosclerosis, Thrombosis, and Vascular Biology

CLINICAL AND POPULATION STUDIES

Ultrasensitive Troponin I and Incident Cardiovascular Disease

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BACKGROUND: To examine the association of ultrasensitive cTnI (cardiac troponin I) with incident cardiovascular disease events (CVDs) in the primary prevention setting.

METHODS: cTnI was analyzed in the baseline plasma (2008–2012) of CVD-free volunteers from the Paris Prospective Study III using a novel ultrasensitive immunoassay (Simoa Troponin-I 2.0 Kit, Quanterix, Lexington) with a limit of detection of 0.013 pg/mL. Incident CVD hospitalizations (coronary heart disease, stroke, cardiac arrhythmias, deep venous thrombosis or pulmonary embolism, heart failure, or arterial aneurysm) were validated by critical review of the hospital records. Hazard ratios were estimated per log-transformed SD increase of cTnI in Cox models using age as the time scale.

RESULTS: The study population includes 9503 participants (40% women) aged 59.6 (6.3) years. cTnI was detected in 99.6% of the participants (median value=0.63 pg/mL, interquartile range, 0.39–1.09). After a median follow-up of 8.34 years (interquartile range, 8.0–10.07), 516 participants suffered 612 events. In fully adjusted analysis, higher cTnI (per 1 SD increase of log cTnI) was significantly associated with CVD events combined (hazard ratio, 1.18 [1.08–1.30]). Among all single risk factors, cTnI had the highest discrimination capacity for incident CVD events (C index=0.6349). Adding log cTnI to the SCORE 2 (Systematic Coronary Risk Evaluation) risk improved moderately discriminatory capacity (C index 0.698 versus 0.685; bootstrapped C index difference: 0.0135 [95% CI, 0.0131–0.0138]), and reclassification of the participants (categorical net reclassification index, 0.0628 [95% CI, 0.023–0.102]). Findings were consistent using the US pooled cohort risk equation.

CONCLUSIONS: Ultrasensitive cTnI is an independent marker of CVD events in the primary prevention setting.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: biomarkers ■ cardiovascular disease ■ primary prevention ■ risk ■ troponin

The release of cTnI (cardiac troponin I) or cTnT (cardiac troponin T) in the blood is a marker of myocardium injury, and it is primarily used for the diagnosis of myocardial infarction.[1] With the development of more sensitive assays,[2] cTnI or cTnT has been detected in the blood samples of subjects from the general population, where it is a marker of future cardiovascular disease (CVD) events, primarily coronary heart disease (CHD), heart failure, and stroke.[3–8] Emerging evidence suggests that cTnI or cTnT are also related to atrial fibrillation,[9–11] whereas association with venous thromboembolism,[12] and abdominal aortic aneurysms[13] has been reported for cTnT only. Most prior studies used high-sensitivity assays to detect cTn as low as 1.90 or 1.20 pg/mL.[3–9,11–13] The ultrasensitive assay Erenna from Singulex is able to detect cTn concentration as low as 0.04 to 0.2 pg/mL, and associations between higher cTnI as measured by this ultrasensitive assay and incident CVD events have been reported in three community-based prospective studies.[14–16] A new ultrasensitive assay SIMOA from QUANTERIX now permits to measure cTnI concentrations as low as 0.013 pg/mL, but to our best knowledge, the clinical relevance of cTnI as measured with this new ultrasensitive assay for CVD risk evaluation in the population has not been

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Nonstandard Abbreviations and Acronyms

cTn	cardiac troponin
NRI	net reclassification index
NT-proBNP	N terminal pro-brain natriuretic peptide
PPS3	Paris Prospective Study III
SCORE 2	Systematic Coronary Risk Evaluation

investigated yet. To address this question, we examined the correlation of ultrasensitive cTnI with major cardiovascular risk factors, quantified its association with incident CVD events and its subtypes including CHD, stroke, cardiac arrhythmias, venous thromboembolism, heart failure, and arterial aneurysms hospitalizations and evaluated its potential added value for CVD risk prediction beyond established risk factors. These questions were addressed in a French prospective community-based cohort, the PPS-3 (Paris Prospective Study III).[17]

Highlights

- cTnI (cardiac troponin I) is released in the blood in the absence of clinical manifestations of cardiovascular disease.
- In this community-based study, cardiac troponin I could be detected in 99.6% of the samples using a new ultrasensitive assay (Simoa Troponin-I 2.0 Kit, Quanterix, Lexington).
- Higher cTnI at baseline was independently associated with a large spectrum of incident cardiovascular disease events over 8 years of follow-up.
- Adding cardiac troponin I to a model base incorporating established risk factors improved significantly albeit moderately cardiovascular disease risk prediction.

METHODS

The design and main objectives of the PPS-3 were published previously.[17] Briefly, PPS-3 is an ongoing community-based prospective study to explore novel biomarkers of sudden cardiac death and other CVD phenotypes in the general population. From June 13, 2008 to May 31, 2012, 10 157 participants aged 50 to 75 years were recruited in a large preventive medical center, the Centre d'Investigations Préventives et Cliniques in Paris (France), which offers a free medical examination every 5 years to working and retired employees (and their families) registered in the French National Insurance System for Salaried Workers. This is one of the largest preventive medical centers in France with 25 000 visits per year. The target population of the Centre d'Investigations Préventives et Cliniques includes 11 million inhabitants from Paris and its surrounding suburbs, which minimizes selection bias towards higher-income or more educated participants. All participants underwent a complete clinical examination coupled with standard biological tests. A self-administered questionnaire gathered information about socioeconomic status, lifestyle, personal and family medical history, including CVD history (previous myocardial infarction, angina, or stroke), current health status, and use of medication.

Biomarker Assessment at Baseline

Blood samples were collected at study recruitment following overnight fasting and immediately centrifuged, aliquoted, and temporarily stored at −80 °C onsite at the medical laboratory of the Centre d'Investigations Préventives et Cliniques center before permanent storage at the PPS-3 biobank at the Georges Pompidou European Hospital, Paris. All measurements of IL (interleukin)-6, hs-CRP (hypersensitive C-reactive protein), NT-proBNP (N-terminal pro-brain natriuretic peptide), and cTnI were analyzed on samples thawed for the first time, using plasma EDTA. They were performed at a public Institut National de la Santé et de la Recherche Médicale Cytometry and Immunobiology core facility Iso 9001 certified at the Cochin Institute (Paris, France) by technicians who were blinded to the clinical and outcome data.[18]

cTnI was analyzed using the Simoa Troponin-I 2.0 Kit (Quanterix, Lexington), which is an ultrasensitive assay and single molecule array technology that is fully automatic. The analytical performances of this assay include a limit of detection of 0.013 pg/mL, a limit of quantification of 0.079 pg/mL, an upper dynamic range of 1200 pg/mL, and a total coefficient of variation <10% at 2.0 pg/mL.[19] High-sensitivity CRP was assessed using the V-plex Human CRP Kit (reference K151STD) from Meso Scale Discovery (Rockville, MD). IL-6 and NT-proBNP were quantified using a MULTI-SPOT 4 Spot Special Order Human Triplex of Customized Kit (reference N45JA-1), which included IL-6 and NT-proBNP, from Meso Scale Discovery.[18]

Baseline Covariates

Smoking status distinguished between current and noncurrent smokers. Education level distinguished between participants with university-level education (minimum bachelor's degree) or equivalent and participants without this level of education. Participants' use of medications was validated during a face-to-face interview with a physician. Prevalent CVD, including past history of stroke, myocardial infarction, or angina pectoris, was self-reported. Body mass index was calculated as kg/m^2. Diabetes was defined as a fasting glucose concentration of ≥126.0 mg/dL (7.0 mmol/L), a nonfasting glucose concentration of ≥200.0 mg/dL (11.1 mmol/L), or the use of antidiabetic treatment. Blood pressure measurements were performed after 10 minutes of rest with the subject in decubitus, and hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive treatment. The glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.[20] The new European SCORE 2 (Systematic Coronary Risk Evaluation) together with the recalibrated (using the local 10-year baseline CVD-free survival rate) US pooled cohort risk equation were used to estimate the 10-year CVD risk of the cohort.[21,22]

Follow-Up and Clinical End Points

Any reported hospitalization for a CVD event on the biennial questionnaire was thereafter validated by an event validation team composed of epidemiologists, cardiologists, neurologists, and cardiac surgeons who were blinded to baseline

data and who critically reviewed hospital discharge records. Non-fatal CHD events included acute coronary syndrome (ie, unstable angina, non–ST-segment–elevation myocardial infarction, and ST-segment–elevation myocardial infarction), hospitalized angina pectoris requiring coronary revascularization procedures, revascularization procedures including coronary artery bypass graft or percutaneous coronary interventions or surgical coronary artery bypass graft. Hospitalized stroke included ischemic, hemorrhagic, transient ischemic attack, and undetermined stroke. All stroke events had brain imaging data available (magnetic resonance imaging and cerebral tomodensitometry). Cardiac arrhythmias included supraventricular arrhythmias (atrial fibrillation, atrial flutter, and junctional tachycardia), ventricular tachycardia, and ventricular fibrillation. Aorto-iliac, femoral, and popliteal arterial aneurysms requiring surgery (graft surgery or stenting) were counted. Diagnosis of deep venous thrombosis or pulmonary embolism required positive imaging tests, including venous Doppler imaging, tomodensitometry, or magnetic resonance imaging scans. Heart failure (HF) was defined according to physical examination signs and symptoms, diagnostic imaging tests that included an evaluation of the ejection fraction (EF), blood biomarkers, and medication use as reported in the hospital discharge records of each index HF hospitalization. HF with preserved EF, with HF reduced EF and borderline HF were defined according to the 2016 European Society of Cardiology guidelines.[23] As of September 30, 2020, the average retention rate for the follow-up was 85%. All-cause mortality status was obtained from the mortality records at the National Institute of Statistics and Economic Studies.

Study Sample Size and Study Population

As shown in the study flowchart (Figure 1), of the 10 157 participants initially recruited for the PPS-3 and after the exclusion of participants with a personal history of CVD (n=315), unmeasured cTnI due to hemolysis or broken tubes (n=64), and missing covariates (n=275) at baseline, 9503 participants were ultimately considered for descriptive purposes. After excluding those participants with no follow-up (between 510 and 540 participants according to the examined event), the study sample size for the prospective analysis ranged from 8907 (CVD events combined) to 8993 (CHD events) according to the studied event.

Ethical Considerations

PPS-3 received institutional support from Institut National de la Santé et de la Recherche Médicale (No. C07-39), and it is registered at the World Health Organization international clinical trial registry platform (https://www.clinicaltrials.gov; Unique identifier: NCT00741728). The study complies with the Declaration of Helsinki, the Ethics Committee of the Cochin Hospital (Paris) approved the study protocol, and participants were included after providing informed consent.

Data Sharing

The data that support the findings of this study cannot be shared publicly due to the privacy of individuals that participated in the study. However, the data can be made available from the corresponding author upon reasonable request.

Statistical Analysis

Descriptive Analysis

For descriptive purposes, cTnI concentrations were divided into prespecified quintiles that were calculated in the whole population. Undetectable concentrations were set at the limit of detection (ie, 0.013 pg/mL). The baseline characteristics of the population by quintiles of cTnI concentrations are reported as the means (SD) for continuous variables and proportions for categorical variables. Values were compared using ANOVA and the Pearson χ^2 test.

Association of cTnI With Incident Events

Unadjusted Kaplan-Meier curves by quintiles of cTnI concentrations (CVD events combined and its subtypes including CHD, stroke, cardiac arrhythmias, thromboembolism), and for the fifth versus the first fourth quintiles of cTnI (arterial aneurysms and heart failure to overcome the small number of events, respectively n=30 and n=29) were plotted using time-to-event as the time scale and compared using the log-rank test. The association between log-transformed cTnI (to correct for skewness, per log-transformed SD increase) and incident CVD events combined and its subtypes were examined in separate Cox proportional hazards model with age as the time scale. The Cox proportional hazards assumption was verified by the weighted Schoenfeld residuals. The absence of departure from linearity was verified graphically by penalized B splines curve and a Loess curve representing the multivariable-adjusted association of cTnI I across its entire range (Figure S1). Time-to-event corresponds to the time elapsed between age at baseline and age at event onset (for the index case), age at death, or age at the last answered questionnaire, whichever occurred first. On the basis of the existing literature, analyses were adjusted for baseline covariates including sex, education level, smoking status, systolic blood pressure, glomerular filtration rate, total and HDL cholesterol, type 2 diabetes, lipid and blood pressure–lowering drugs, IL-6, and NT-proBNP. Analyses were also adjusted for antiarrhythmic (Anatomical Therapeutic Chemical Classification System code C01B [class I and III antiarrhythmic] and C07 [beta-blockers]) and antithrombotic drugs (Anatomical Therapeutic Chemical Classification System code B01A) when examining CVD events combined or cardiac arrhythmias, and antithrombotic drugs (Anatomical Therapeutic Chemical Classification System code B01A) when examining thromboembolism events. Also based on the existing literature, interactions between cTnI and sex, smoking status, lipid-lowering medication use at baseline, and CVD events combined were evaluated one at a time by including a multiplicative interaction term in the fully adjusted Cox model. In a secondary analysis, we considered death as a concurrent event and run a competing risk analysis using the Fine and Gray method. Also, to assess reverse causality, the analysis was repeated after excluding CVD events that occurred in the first 2 years of follow-up. We further checked whether the association of cTnI with CVD events combined differed according to the baseline CVD risk as estimated by the European SCORE 2 risk[21] and the recalibrated US pooled cohort risk equation.[22] We, therefore, performed stratified analysis between participants who were at low (<5%), moderate (5%–10%), and high risk (≥10%) according to the European SCORE 2 risk and repeated this

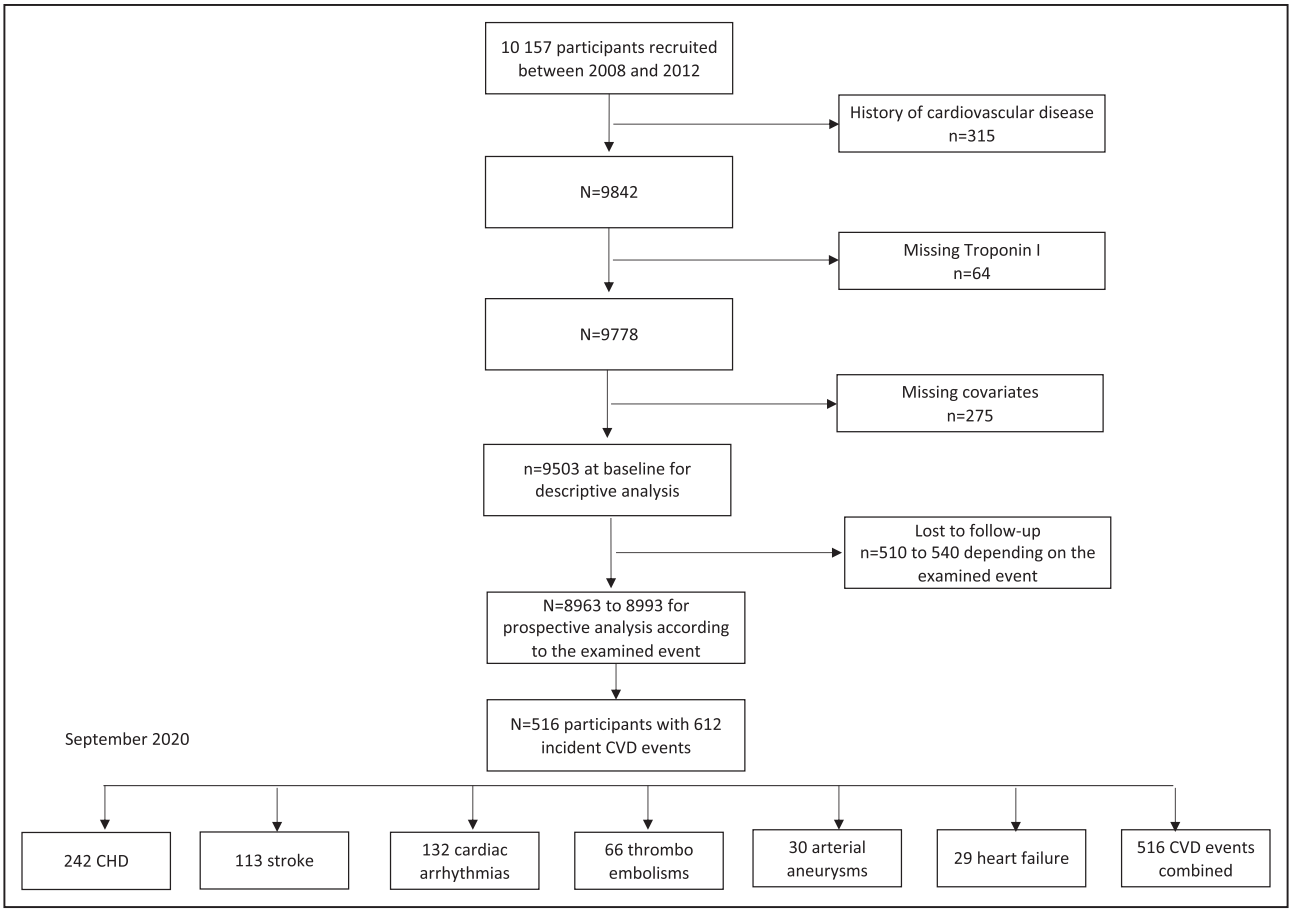

Figure 1. Study flow chart.
CHD indicates coronary heart disease; and CVD, cardiovascular disease.

analysis among those who had a 10-year risk <7.5%, between 7.5% and 20%, and equal or above >20% according to the US pooled cohort risk equation, respectively.

Added Value of cTnI for CVD Risk Prediction

For this analysis, follow-up was censored at 10 years. Discrimination capacity was assessed by the Harell C index. We first provided the Harell C index for CVD events combined associated with log cTnI, each single risk factor comprising the SCORE 2 algorithm, hs-CRP, IL-6, and NT-proBNP. Then we compared the discrimination capacity of the SCORE 2 algorithm with and without log cTnI. The average difference in the Harell C index of SCORE 2 algorithm with and without log cTnI and the corresponding 95% CIs were estimated after 1000 bootstrapping. We also calculated the categorical and continuous net reclassification index (NRI), using the 10-year risk categories of the SCORE 2 algorithm (<5%, 5%–10%, >10%) for the categorical NRI. Finally, we calculated the categorical and continuous NRI among those at intermediate risk (clinical NRI). This approach was repeated using the US recalibrated pooled cohort risk equation and the corresponding risk categories. In addition, we calculated the negative predictive value of ultra-low levels of cTnI (first quintile of the distribution) to predict CVD events combined.

All analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Baseline Characteristics

The study population includes 9503 CVD-free participants who had no missing data on troponin I concentrations and covariates (Figure 1). The baseline characteristics of the excluded and included participants are reported in Table S1.

The mean (SD) age was 59.6 (6.3) years, and 40% were females. There were 41 participants with undetectable cTnI so that cTnI was detected in 99.6% (9462 out of 9503 participants) of the study population. The median value was 0.63 pg/mL (interquartile range, 0.39–1.09), and 90% of the study participants (n=8561) had cTnI concentrations below 1.90 pg/mL, which was the limit of detection most often used in prior studies. The baseline characteristics of the population according to the quintiles of cTnI concentrations are reported in Table 1. Participants with higher cTnI concentrations were more often male, older, had worse lifestyle, and cardiovascular risk profiles but were more educated and had lower total cholesterol levels. They were more often exsmokers and less often current smokers, but heavy smokers (≥15 pack-years) were more often found in higher quintiles of cTnI. The

Table 1. Baseline Characteristics According to Quintiles of Troponin-I

		Quintiles of troponin I concentrations pg/mL					
	Overall	0.013–0.340	0.340–0.527	0.527–0.766	0.766–1.247	1.247–1321.52	
	N=9503	N=1900	N=1901	N=1901	N=1901	N=1900	*P* value
Troponin I, pg/mL	0.63 (0.39–1.09)	0.23 (0.17–0.29)	0.43 (0.39–0.48)	0.63 (0.58–0.70)	0.95 (0.85–1.09)	1.89 (1.49–2.77)	<0.0001
Age at inclusion, y	59.56 (6.29)	57.63 (5.45)	58.73 (5.87)	59.30 (5.96)	60.36 (6.38)	61.80 (6.90)	<0.0001
Sex, male	5759 (60.60)	674 (35.47)	966 (50.82)	1182 (62.18)	1362 (71.65)	1575 (82.89)	<0.0001
High education level	3749 (39.45)	690 (36.32)	741 (38.98)	750 (39.45)	780 (41.03)	788 (41.47)	0.01
Smoking status							
Never smoked	4911 (51.68)	1003 (52.79)	1014 (53.34)	975 (51.29)	993 (52.24)	926 (48.74)	<0.0001
Exsmokers	3082 (32.43)	534 (28.11)	577 (30.35)	639 (33.61)	626 (32.93)	706 (37.16)	<0.0001
Current smoker	1510 (15.89)	363 (19.11)	310 (16.31)	287 (15.10)	282 (14.83)	268 (14.11)	<0.0001
Pack-years status*							
0 (never smoked)	4911 (53.34)	1003 (54.04)	1014 (54.90)	975 (52.67)	993 (54.11)	926 (50.94)	0.10
<15, light smokers	2613 (28.38)	542 (29.20)	512 (27.72)	538 (29.07)	502 (27.36)	519 (28.55)	0.10
≥15: heavy smokers	1683 (18.28)	311 (16.76)	321 (17.38)	338 (18.26)	340 (18.53)	373 (20.52)	0.10
Systolic blood pressure, mm Hg	131.08 (16.33)	125.06 (14.58)	128.09 (14.74)	130.95 (15.33)	133.99 (16.09)	137.33 (17.82)	<0.0001
Blood pressure–lowering drug	1402 (14.75)	159 (8.37)	209 (10.99)	251 (13.20)	329 (17.31)	454 (23.89)	<0.0001
Body mass index, kg/m^2	25.16 (3.70)	24.20 (3.74)	24.68 (3.62)	25.15 (3.63)	25.64 (3.64)	26.12 (3.57)	<0.0001
Total cholesterol, mg/dL	221.62 (35.84)	225.23 (35.25)	223.86 (36.41)	222.54 (36.44)	219.71 (34.92)	216.75 (35.54)	<0.0001
HDL cholesterol, mg/dL	58.42 (15.23)	61.76 (15.94)	59.58 (15.60)	57.80 (15.16)	57.27 (14.63)	55.71 (14.03)	<0.0001
Lipid-lowering drug	1236 (13.01)	189 (9.95)	208 (10.94)	221 (11.63)	271 (14.26)	347 (18.26)	<0.0001
Type 2 diabetes	397 (4.18)	58 (3.05)	61 (3.21)	63 (3.31)	92 (4.84)	123 (6.47)	<0.0001
CKD-EPI, mL/(min·1.73 m^2)	83.62 (12.28)	86.10 (11.69)	84.50 (11.75)	83.88 (11.98)	82.93 (12.28)	80.67 (13.03)	<0.0001
Interleukine 6, pg/mL	0.60 (0.45–0.83)	0.55 (0.42–0.76)	0.57 (0.44–0.80)	0.60 (0.45–0.82)	0.63 (0.46–0.85)	0.66 (0.49–0.91)	<0.0001
NT-proBNP, pg/mL	217.60	192.07	202.23	209.55	221.28	273.58	<0.0001
	(107.18–430.24)	(96.06–374.56)	(104.09–395.77)	(101.59–421.56)	(112.50–420.83)	(134.85–569.71)	
SCORE 2 risk, %†	4.39 (3.06–6.37)	3.33 (2.24–4.76)	3.87 (2.78–5.53)	4.31 (3.13–6.01)	4.94 (3.58–6.93)	5.92 (4.15–8.39)	<0.0001
SCORE 2 risk category†							
Low (<5%)	5303 (59.54)	1387 (77.79)	1225 (68.94)	1103(61.35)	909 (50.95)	679 (38.47)	<0.0001
Moderate (<10%)	3083 (34.61)	364 (20.42)	512 (28.81)	620 (34.48)	752 (42.15)	835 (47.31)	<0.0001
High (≥10%)	521 (5.85)	32 (1.79)	40 (2.25)	75 (4.17)	123 (6.89)	251 (14.22)	<0.0001
Recalibrated pooled risk equation, %†	6.46 (3.63–11.22)	3.99 (2.13–6.88)	5.21 (3.13–9.01)	6.33 (3.79–10.37)	7.87 (4.74–12.80)	10.37 (6.06–16.56)	<0.0001
Recalibrated pooled risk equation category†							
Low (<7.5%)	5094 (57.19)	1391 (78.01)	1195 (67.25)	1065 (59.23)	839 (47.03)	604 (34.22)	<0.0001
Moderate (<20%)	3211 (36.05)	363 (20.36)	540 (30.39)	647 (35.98)	791 (44.34)	870 (49.29)	<0.0001
High (≥20%)	602 (6.76)	29 (1.63)	42 (2.36)	86 (4.78)	154 (8.63)	291 (16.49)	<0.0001

Troponin I was measured using a novel ultrasensitive assay and single molecule array technology (Simoa Troponin-I 2.0 Kit, Quanterix, Lexington), with a limit of detection as low as 0.013 pg/mL. Quintiles of troponin I were calculated in the whole population; renal function was estimated using the CKD-EPI formula (20). CHD indicates coronary heart disease; CKD-EPI equation, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; and SCORE, Systematic Coronary Risk Evaluation.

*There were 296 participants with missing data on pack-years.

†SCORE 2 risk (21) and the US pooled cohort risk equation (22) compute the probability of cardiovascular disease events at 10 y; therefore, the 10-y CVD risk was estimated only among those who had follow-up, which was censored at 10 y.

average 10-year CVD risk as estimated by the SCORE 2 risk or the US recalibrated pooled cohort risk equation increased with the baseline concentrations of cTnI.

Baseline cTnI and Incident Events

During a median follow-up period of 8.34 to 8.55 years (interquartile range, 8.0–8.03, 10.05–10.07), 516 participants had 612 incident and hospitalized CVD events. These included 242 incident CHDs, 113 incident strokes (103 ischemic events, including 45 transient ischemic attacks, 8 hemorrhagic events, and 1 undetermined), 132 incident cardiac arrhythmias (101 atrial fibrillation, 16 flutter, 11 junctional tachycardia, and 4 ventricular tachycardia–ventricular fibrillation), 66 incident thromboembolisms (42 pulmonary embolisms, 24 deep venous thromboses,

and 3 combined), 30 incident arterial aneurysms (26 aortic aneurysms, including 11 in the abdominal aorta, 10 in the thoracic aorta and 5 on the iliac artery, 2 femoral, and 2 popliteal aneurysms), and 29 incident heart failure events (16 HF reduced EF, 3 HF with preserved EF, 7 with borderline EF, and 3 with undetermined EF). In addition, 278 died during follow-up (Figure 1). The unadjusted Kaplan-Meier curves were consistent with a gradient of incidence rates across the quintiles of cTnI concentrations for CVD events combined, CHD, stroke, cardiac arrhythmias, and thromboembolisms (Figure 2A through 2E), and with substantial difference in the incidence rates of heart failure and arterial aneurysms between participants from the top versus the bottom 4 quintiles of troponin I (Figure S2). In the fully adjusted analysis accounting for sociodemographic factors, CVD risk factors, blood biomarkers IL-6 and NT-proBNP, higher cTnI (per 1 SD increase of log cTnI) was significantly associated with CVD events combined, CHD, cardiac arrhythmias, and thromboembolism (Table 2). The association with incident stroke was in the expected direction but did not reach statistical significance. High cTnI (fifth versus first 4 quintiles of cTnI) was also related to incident heart failure and aortic aneurysms (Table S2). The association between cTnI and CVD events combined did not differ significantly with sex (*P* value for interaction=0.63), smoking status (*P* value for interaction=0.88), or lipid-lowering medication at baseline (*P* values for interaction=0.19). Furthermore, in multivariable analysis, cTnI was unrelated to all-cause mortality (hazard ratio [HR] per 1 SD log cTnI, 1.10 [95% CI, 0.96–1.25]). In competing risk analysis with death as a concurrent event, the association between higher cTnI and the examined outcomes remained unchanged, the HR (per 1 SD log cTnI) for incident CVD event combined being: HR, 1.18 (95% CI, 1.07–1.32). In addition, the association between higher cTnI and incident CVD events remained consistent (HR per 1 SD log cTnI, 1.12 [95% CI, 1.00–1.25]) after excluding the 114 early CVD events that occurred in the first 2 years of follow-up.

Stratified Analysis According to the 10-Year Risk of Cardiovascular Disease

A total of 59%, 33%, and 6% of the study participants had a 10-year CVD risk that was estimated to be low, moderate, and high, according to the SCORE 2 algorithm, with very similar distribution when using the US pooled cohort risk equation. In stratified analysis, higher cTnI concentrations (per 1 SD increase of log cTnI) remained associated with CVD events combined in the 3 risk strata (*P* for interaction=0.33 with SCORE 2 risk and *P*=0.24 with the US pooled cohort risk equation; Figure 3).

Added Value of Baseline cTnI for Cardiovascular Disease Risk Prediction

Univariate Cox analysis indicates that compared with each single risk factor, log cTnI had the highest discrimination capacity for incident CVD events combined (C index=0.6349), followed by systolic blood pressure (C index=0.6078), whereas age and sex had the fourth and fifth higher discriminatory capacity (Figure 4). Adding log

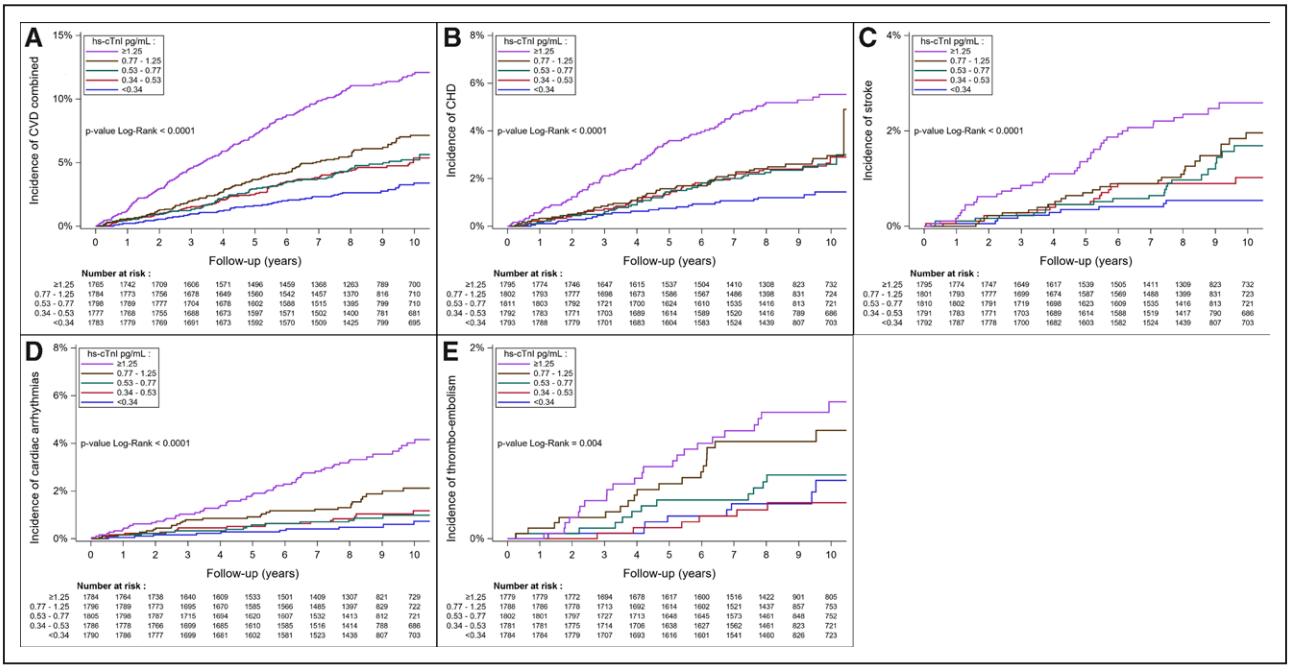

Figure 2. Kaplan-Meier curves of incident cardiovascular disease events by quintiles of cTnI (cardiac troponin I) concentration. Study outcomes include CVD events combined (**A**), CHD events (**B**), stroke events (**C**), cardiac arrhythmias (**D**), and thrombo-embolism (**E**). Incident rates are compared using the log-rank test. CHD indicates coronary heart disease; CVD, cardiovascular disease; and hs-cTnI, hypersensitive cardiac troponin I.

Table 2. Association Between cTnI Concentration and Incident CVD Events

Troponin I concentration in pg/mL	n/N	Unadjusted HR (95% CI)	Fully adjusted HR (95% CI)*
CVD combined			
Per 1 SD log troponin I	516/8907	1.39 (1.29–1.50)	1.18 (1.08–1.30)
Per 1 SD log troponin I	242/8993	CHD 1.45 (1.30–1.61)	1.21 (1.06–1.39)
Stroke			
Per 1 SD log troponin I	113/8989	1.23 (1.03–1.61)	1.05 (0.85–1.29)
Cardiac arrhythmias			
Per 1 SD log troponin I	122/8961	1.50 (1.31–1.71)	1.26 (1.07–1.50)
Venous thromboembolism			
Per 1 SD log troponin I	66/8934	1.33 (1.06–1.66)	1.29 (1.00–1.66)

Troponin I was measured using a novel ultrasensitive assay and single molecule array technology (Simoa Troponin-I 2.0 Kit, Quanterix, Lexington), with a limit of detection as low as 0.013 pg/mL. Arrhythmic events included hospitalized atrial fibrillation, flutter, ventricular tachycardia and fibrillation, and junctional tachycardia. HRs and 95% CIs were estimated in separate Cox proportional hazard models using age as the time scale. HRs were adjusted for sex, and baseline education level, systolic blood pressure, smoking status, glomerular filtration rate, total and HDL cholesterol, type 2 diabetes, lipid-lowering and blood pressure–lowering drugs, NT-proBNP and IL-6. The analysis was further adjusted for antiarrhythmic and antithrombotic drugs when investigating arrhythmic events or CVD events combined and for antithrombotic drugs when examining thromboembolism. CHD indicates coronary heart disease; CVD, cardiovascular disease; HR, hazards ratios; hs-cTnI, hypersensitive cardiac troponin I; IL, interleukin; and NT-proBNP, N-terminal pro-brain natriuretic peptide.

cTnI to the SCORE 2 algorithm increased significantly albeit moderately discriminatory capacity (C index 0.698 versus 0.685; bootstrapped C index difference, 0.0135 [95% CI, 0.0131–0.0138]), and reclassification of the participants: categorical NRI, 0.0628 (95% CI, 0.0230–0.102) and continuous NRI, 0.264 (95% CI, 0.175–0.353), respectively (Table S3A). Among the participants at moderate risk, the addition of log cTnI improved reclassification of the participants (continuous NRI, 0.213 [95% CI, 0.087–0.340]; categorical NRI, 0.049 [95% CI, —0.0460 to 0.1039]; Table 3). Very consistent findings were noted when using the US recalibrated pooled cohort risk equation (Table 3 and Table S3B). Ultra-low levels of cTnI (first quintile of the distribution) had a negative predictive value for the CVD events combined of 97.2% (95% CI, 96.4–97.9; Table S4).

DISCUSSION

In this community-based prospective cohort of 9503 CVD-free participants, the clinical relevance of cTnI as measured by a novel ultrasensitive assay (Simoa, Quanterix, Lexington) for predicting incident CVD events was examined for the first time. Three main findings were noted: cTnI could be detected in 99.6% of the samples; higher cTnI was independently associated with incident CVD events; and adding cTnI to a model base incorporating established risk factors improved CVD risk prediction moderately.

With this new ultrasensitive assay, 99.6% of cTnI concentrations could be detected in the present study as compared to 65% to 85% in the majority of prior studies that employed high-sensitive assays.[3–9,11–13] The extremely low level of cTnI detected by this ultrasensitive assay might be considered as noise but the correlation between cTnI and most cardiovascular risk factors renders this assumption unlikely. Using another ultrasensitive assay (Erenna, Singulex), detection rates similar to ours were reported in the MONICA-KORA,[14] whereas lower detection rates were reported in FINRISK (National FINRISK Study) and Framingham (93.9% and 81%, respectively).[15,16]

We further expand the results of previous community-based studies by extending the spectrum of CVD events for which the association with cardiac troponin has been studied scarcely. Accordingly, this is the first study on cTnI and incident venous thromboembolism, which complements the only prior existing study on cTnT and incident venous thromboembolism combining data from the ARIC (Atherosclerosis Risk in Communities) and the Cardiovascular Health Study.[13] Although acute atherosclerotic diseases or risk factors are established determinants for venous thromboembolism and pulmonary embolism, less is known regarding chronic atherosclerotic diseases. The currently reported association with cTnI suggests that early signs of myocardial injury may contribute to the onset of venous thromboembolism and pulmonary embolism. This finding is also consistent with previous studies showing cardiac troponin I to be useful for risk stratification in patients with venous thromboembolism.[24,25] This is also the first study on cTnI and incident arterial aneurysms, which complements the only prior existing study on cTnT and incident abdominal artery aneurysms in ARIC.[14] The associations with arterial aneurysms in both studies were independent from traditional risk factors, but we additionally demonstrated that they were independent from IL-6 and NT-proBNP, 2 biomarkers that were previously related to incident abdominal artery aneurysms.[26,27] The association of higher cTnI with arterial aneurysm might be due to coronary perfusion impairment, which is secondary to the systemic vascular resistance characterizing arterial aneurysm,

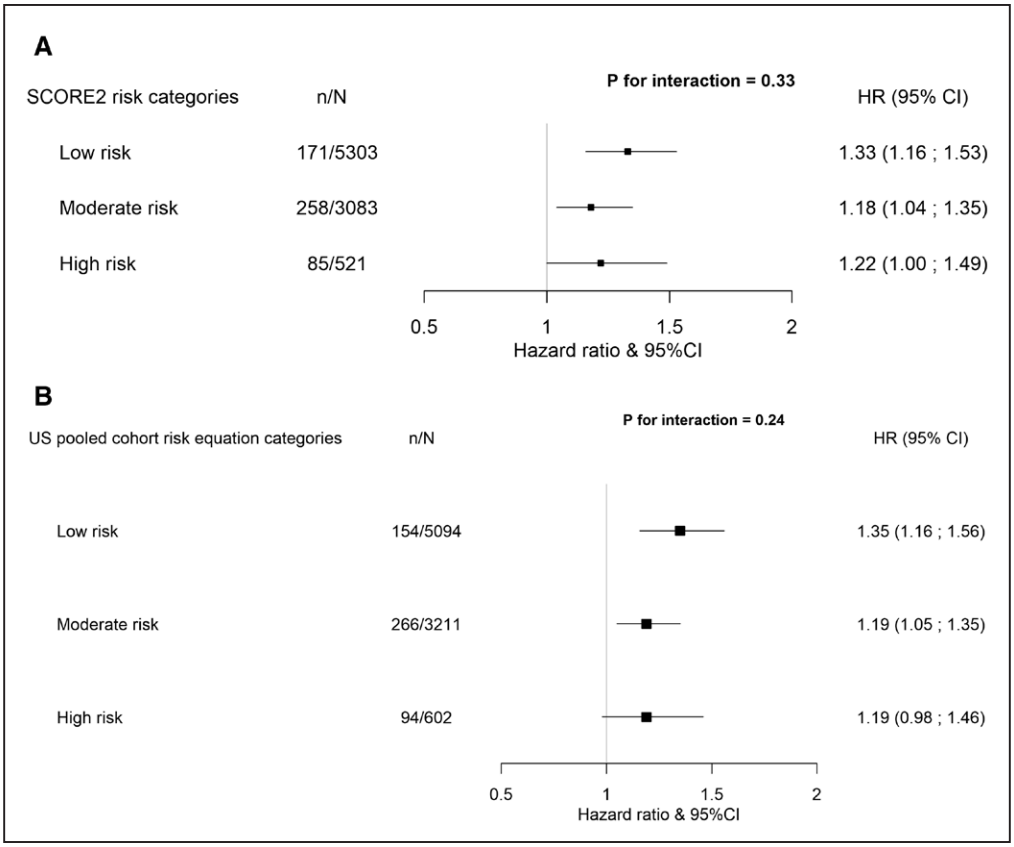

Figure 3. Association of cardiac troponin I with incident cardiovascular disease events stratified by 10-year risk of cardiovascular disease was estimated by the European SCORE 2 (Systematic Coronary Risk Evaluation; A) and by the recalibrated US pooled cohort risk equation (B).

SCORE 2 risk computes the probability of cardiovascular disease events at 10 years using age, smoking status, systolic blood pressure, total and HDL (high-density lipoprotein) cholesterol, type 2 diabetes and product interaction terms with age as covariates.[21] The US pooled cohort risk equation computes the probability of cardiovascular disease events at 10 years using age, smoking status, systolic blood pressure, total and HDL cholesterol, type 2 diabetes, antihypertensive drug medication, and product interaction terms with age as covariates.[22] In each stratum, hazard ratios (HRs) and 95% CIs were estimated by Cox proportional hazard models using age as the time scale, and analysis was adjusted for sex, antiarrhythmic, and antithrombotic drugs at baseline. The hazard ratios are given per 1 SD increase in the natural logarithm of troponin I.

but further studies are needed to clarify the underlying mechanisms of this association.[28] The significant association between cTnI and incident cardiac arrhythmias in the present study complements the emerging evidence suggesting association between cTnI and incident atrial fibrillation in the Framingham study[11] and the Busselton health study in Australia[12] and between cTnT and incident atrial fibrillation in the ARIC study.[9] The reported associations between cTnI and CHD or heart failure in the current study are consistent with the results of several large prospective community-based cohorts and meta-analyses.[3–5] Contrary to previous studies,[6–8] the association between higher cTnI and incident stroke did not reach statistical significance in fully adjusted analysis, potentially due to a lack of power and to the burden of transient ischemic attack, which represented 40% of stroke cases in the present study.

cTnI had the highest discriminatory capacity for CVD events among the single risk factors, and the related C statistic (ie, 0.6349) was closed to values observed when applying existing risk prediction algorithms.[29] This indicates that cTnI alone already explained a large variance of the CVD risk, and may suggest that cTnI can be viewed as an integrative marker of CVD. This is consistent with the correlations between cTnI and several established risk factors, together with the association of cTnI with several CVD phenotypes in the present study. This may also explain why combining cTnI with established risk factors improved CVD risk prediction moderately, a finding previously reported in studies using high-sensitive assays[3,4,6,8] and ultrasensitive assays.[14,15] Still, that the addition of cTnI to established risk factors improved significantly (although moderately) the reclassification of participants who are at moderate CVD risk (clinical NRI) may carry clinical implications for CVD risk stratification. Indeed, emerging evidence suggests that statin therapy is associated with cardiac troponin concentration reduction and that cardiac troponin concentration reduction translates into a CVD risk reduction.[30] Nonpharmacological interventions, such as moderate physical activity and weight control, have also been shown to modulate cardiac troponin concentrations.[31,32] Also, that cTnI remains

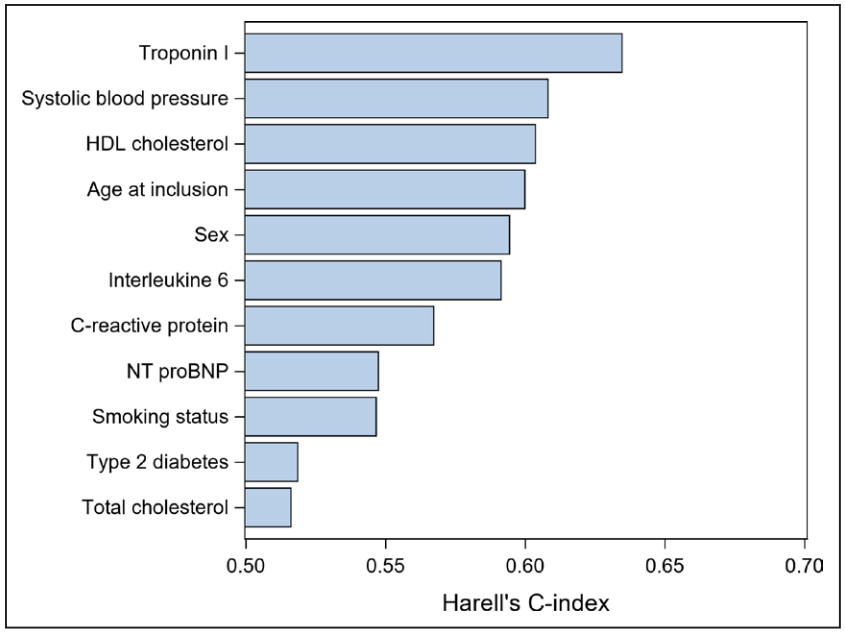

Figure 4. Discrimination capacity for cardiovascular disease events of log-transformed cardiac troponin I and each single risk factor.
For each risk factor, the discriminatory capacity was computed in univariate Cox analysis and estimated using the Harell C index.

associated with CVD events combined even in subjects who were at low CVD risk, which represented between 57% and 59% of the study participants according to the risk equation used, further suggests that cTnI measurement is a sensitive marker to newly identify a group of at-risk participants who would be inappropriately classified as being at low risk on the basis of classical risk factors only. Taken together, the current findings support recent simulation studies suggesting that screening for classical risk factors and cTnI in the general population versus screening for classical risk factors only would be cost-effective for preventing CVD events, premature death, and productivity losses.[33]

We acknowledge the following limitations. Repeated measurements of cTnI concentrations were not available whereas serial measurements of troponin have been related to CVD onset.[30,34] Although participants with self-reported prevalent CVD were excluded, reverse causation due to undetected asymptomatic CVD cannot be ruled out, but sensitivity analysis excluding early CVD events provided consistent findings. As in any observational study, residual confounding due to unmeasured risk factors cannot be excluded. Only hospitalized events were analyzed, so that outcomes, such as transient cardiac arrhythmias, paucisymptomatic thromboembolic events, and transient ischemic attack, which are managed in outpatient settings, were missed. At the time of analysis, we had not been granted access to the national French registry of the causes of death, hence, cause-specific mortality, and CVD mortality in particular could not be investigated. The apparent lack of association between cTnI and all-cause mortality is likely hiding an

Table 3. Added Value of cTnI Concentration for 10-Year CVD Risk Prediction Beyond Established Risk Factors Contained in SCORE 2 Risk and US Pooled Cohort Risk Equation

Models	Bootstrapped Harell C index (SD)	Bootstrapped delta C index	Continuous NRI	Categorical NRI	Clinical continuous NRI*	Clinical categorical NRI*
	SCORE 2					
Basic model†	0.6849 (0.0004)	0.0134 (0.0130 to 0.0138)	0.2641 (0.1755 to 0.3527)	0.0628 (0.0230 to 0.1025)	0.2138 (0.0868 to 0.3407)	0.0496 (−0.0460 to 0.1039)
+ log cTnI	0.6983 (0.0004)					
	US pooled cohort risk equation					
Basic model‡	0.6906 (0.0004)	0.0092 (0.0088;0.0096)	0.2495 (0.1608 to 0.3382)	0.0402 (0.072 to 0.0732)	0.1951 (0.0702 to 0.3201	0.0499 (−0.0280 to 0.1026)
+ log cTnI	0.6998 (0.0004)					

Troponin I was measured using a novel ultrasensitive assay and single molecule array technology (Simoa Troponin-I 2.0 Kit, Quanterix, Lexington), with a limit of detection as low as 0.013 pg/mL. The average difference in the Harell C index of the SCORE 2/US pooled cohort risk equation with and without log cTnI and the corresponding 95% CIs were estimated after 1000 bootstrapping. The 10-y risk categories of the SCORE 2 algorithm (<5%, 5%–10%, >10%) and of the US pooled cohort risk equation (<7.5%, 7.5%–20%, >20%) were used to estimate the categorical NRI.[21,22] cTnI indicates cardiac troponin I; CVD, cardiovascular disease; NRI, net reclassification index; and SCORE, Systematic Coronary Risk Evaluation.

*The clinical NRI was estimated only among those at intermediate risk according to the SCORE 2 (CVD 10-y risk between 5% and 10%) and the US pooled cohort risk equation (CVD 10-y risk between 7.5% and 20%).

†The SCORE 2 model includes age, smoking status, diabetes, systolic blood pressure, and total- and high-density lipoprotein cholesterol as covariates.

‡The US pooled cohort risk equation includes age, smoking status, diabetes, systolic blood pressure, blood pressure lowering treatment, total- and high-density lipoprotein cholesterol as covariates.

association with CVD mortality. Taken together, the total number of CVD events examined in the present study is likely underestimated. The PPS-3 participants were aged 50 to 75 years and were mostly of White race so that the study results cannot be applied directly to other age and ethnic groups; in particular, differential association between cTnI and CVD by age and by race has been previously shown.[3,5] People who are attending preventive medical centers are more health conscious and are in better health than the general population of same age and sex.[35] This may affect the distribution of cTnI and risk factors in general (ie towards lower values) but not the association between cTnI and CVD events. Finally, the findings on cTnI were obtained from an assay that is currently for research purposes only.

CONCLUSION AND RELEVANCE

In this community-based prospective cohort, cTnI concentrations as measured by a novel ultrasensitive assay could be detected in 99.6% of the population, was associated with a large spectrum of incident CVD events, and improved significantly albeit moderately CVD risk prediction beyond established risk factors.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Figures S1–S2
Major Resources Table
Table S1–S4

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