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Cardiac Troponin I and T Are Associated with Left Ventricular Function and Structure: Data from the Akershus Cardiac Examination 1950 Study

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BACKGROUND: Concentrations of cardiac troponin I (cTnI) and T (cTnT) are associated with clinical cardiac outcomes, but do not correlate closely in subjects recruited from the general population. Accordingly, we hypothesized that cTnI and cTnT concentrations would be influenced by different cardiovascular (CV) and non-CV risk factors and reflect different CV phenotypes.

METHODS: We measured cTnI and cTnT with last generation assays in 1236 women and 1157 men with no known CV disease participating in the prospective observational Akershus Cardiac Examination 1950 Study. All study participants underwent extensive CV phenotyping at baseline, including detailed echocardiography.

RESULTS: Concentrations of cTnI were measurable in 60.3% and cTnT in 72.5% of study participants ($P < 0.001$), and correlated moderately ($r = 0.53$; $P < 0.001$). cTnI was more strongly associated with male sex ($P = 0.018$), higher education ($P < 0.001$), history of hypertension ($P < 0.001$), and age ($P < 0.001$), whereas cTnT was more strongly associated with eGFR ($P = 0.015$). Both cTnI and cTnT were inversely associated with global longitudinal strain and positively associated with LV mass index (LVMI) in analyses adjusted for CV risk factors. The association between cTnI and LVMI was stronger than the association between cTnT and LVMI ($P = 0.035$). Concentrations of cTnI improved diagnostic accuracy for LV hypertrophy when added to established CV risk factors, but concentrations of cTnT did not improve these models further.

CONCLUSIONS: In a large community-based cohort examined with extensive echocardiography, concentrations of cTnI and cTnT are associated with subclinical LV hypertrophy and dysfunction. Concentrations of cTnI appear superior to cTnT in predicting subclinical LV hypertrophy.

Introduction

Troponins are part of the contractile apparatus found in striated muscle, and cardiac troponin (cTn) I (cTnI) and T (cTnT) are specific for the myocardium. In contemporary cardiology, measurement of cTn is an integral part of diagnosing acute coronary syndromes. Increasingly sensitive cTn assays have enabled quantification of small concentrations of cTn in the general population. Several large community-based investigations have documented associations of such concentrations with common cardiovascular (CV) risk factors *(1–4)*, and with the risk of myocardial infarction, heart failure, ischemic stroke, and CV death *(4–6)*. Left ventricular (LV) structure and function are routinely quantified by echocardiography, with estimation of echocardiographic indices such as LV ejection fraction (LVEF) and LV mass [indexed to body surface area; LV mass index (LVMI)]. Global longitudinal strain (GLS) is a novel and sensitive index that seems to be superior to LVEF in assessing subtle alterations in LV systolic function *(7)*. Similar to cTn, GLS predicts CV

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morbidity and death, both in patients with established CV disease *(8)* and in subjects recruited from the general population *(9)*. In the general population, increasing concentrations of cTn are associated with declining LVEF as assessed by cardiac magnetic resonance imaging *(10)* and echocardiography *(11, 12)*.

In the clinical setting, cTnI and cTnT are interchangeable in the diagnostic work-up of acute coronary syndromes. Evidence is however amassing for significant biological differences between these two cTn isoforms. Concentrations of cTnT exhibit circadian variation, in contrast to more stable concentrations of cTnI throughout day and night *(13)*, and concentrations of cTnT and cTnI are only modestly correlated *(14)*. This lack of association may be due to differential processing of cTnT and cTnI once released, as well as differential recognition of native and processed cTn forms by the different assay methods. In community dwellers, cTnI appears more strongly associated with CV events and cTnT with noncardiovascular mortality *(15)*, but concentrations of both cTnI and cTnI may provide independent prognostic information *(16)*.

Accordingly, using a large cohort recruited from the general population examined with state-of-the-art echocardiography, we hypothesized that *(1)* cTnI and cTnT are differentially associated with CV risk factors, LV structure and function, and that *(2)* cTnI and cTnT would provide complementary diagnostic information to established CV risk factors in determining subclinical LV hypertrophy and dysfunction.

Methods

STUDY OVERVIEW

The Akershus Cardiac Examination (ACE) 1950 Study is a prospective, community-based cohort of individuals born in 1950 residing in Akershus County, Norway. The study aims to investigate the development and progression of CV and cerebrovascular disease in an age cohort of middle-aged subjects. The study was conducted at the two hospitals of Akershus County, Norway: Akershus University Hospital and Bærum Hospital/Vestre Viken Hospital Trust. Of 5827 eligible study subjects, 3706 (63.6%) were included and the baseline examination was conducted from September 2012 to April 2015. A more detailed study design has been reported previously *(17)*. The study complies with the Declaration of Helsinki and is approved by the Regional Committee for Medical Research Ethics. All participants provided informed written consent before study commencement.

PARTICIPANTS

Medical history, current medication, and socioeconomic data, including alcohol and tobacco consumption, were obtained at baseline and are based on self-report. Coronary artery disease (CAD) was defined as self-reported history of myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention. Diabetes mellitus was defined as one or more of the following: *(1)* self-reported diabetes, *(2)* use of antidiabetic medication, or *(3)* the combined presence of increased concentrations of HbA1c (≥6.5%) and fasting blood glucose (≥126 mg/dL [≥7.0 mmol/L]) on baseline examination. Hypertension was defined as daily use of antihypertensive medication or baseline systolic blood pressure of ≥140 mmHg or diastolic blood pressure measurement of ≥90 mmHg. Chronic obstructive pulmonary disease was defined as baseline post bronchodilator spirometry FEV1/FVC ratio below the age-dependent lower limit of normal, or by self-report when spirometry data were missing ($n = 4$). Higher education was defined as education at the level of college, university, or equivalent. Participants with known CAD at baseline ($n = 263$) were excluded from the analyses, as well as participants with echocardiographic recordings not appropriate for GLS analyses ($n = 1047$) or with missing biomarker data ($= 3$).

ECHOCARDIOGRAPHY

Transthoracic echocardiography was performed by two echocardiography technicians and four trained fellows using GE Vivid E9 (GE Healthcare) with the M5S probe according to a predefined protocol as recently reported *(18)*. The following views were recorded (four cardiac cycles were recorded during breath hold at end expiration): parasternal long- and short-axis, and apical four-chamber, two-chamber and long-axis. Acquisition was made for standard two-dimensional images as well as M-mode, tissue velocity imaging, pulsed and continuous Doppler, and the images were analyzed with EchoPAC 201 (GE Healthcare). GLS by speckle tracking echocardiography was analyzed semi-automatically by tracing the mid-line myocardium in the three apical views using a 17-segment LV model. Region of interest was adjusted to fit the myocardial thickness. A segment was excluded if it failed to track properly. The whole analysis was excluded if more than one segment per image view, or more than two segments in total, failed to track properly. As previously recommended, we used absolute values of GLS in all analyses (i.e., an increase in absolute values of GLS equaling improving LV function, comparable to LVEF) *(19)*. LVEF was determined using the modified Simpson's biplane method. LV mass was calculated from M-mode measurements and indexed (LVMI) using body surface area by the Mosteller formula *(20)*. Intra- and interobserver variability testing were performed by two observers (E.N.A. and B.K.) in 15 randomly selected patients for GLS (Supplemental Table 1).

BLOOD SAMPLING PROCEDURES AND BIOCHEMICAL ASSAYS

At study baseline, venous blood was sampled in serum, citrate plasma, lithium heparin plasma and ethylenediaminetetraacetic acid (EDTA) plasma collection tubes, centrifuged at room temperature, and frozen in a research biobank at −80°C. Routine hospital laboratory clinical chemistry was used for immediate analyses of hemoglobin, white blood count, HbA1c (all from EDTA whole blood), C-reactive protein (CRP), glucose, cholesterol (total, HDL), triglycerides, and creatinine (all from serum). In the laboratory reports, the limit of detection for CRP varied during the time period of the study baseline examination (<3 mg/L, 2.9 mg/L, and <1 mg/L), any concentration below this limit was designated a value equal to half of the detection limit (i.e., 1.5 mg/L, 1.45 mg/L, and 0.5 mg/L). Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation. cTnI was measured in January 2017 with the ARCHITECT STAT High Sensitive Troponin-I assay (Abbott Diagnostics). Limit of detection (LoD) for this assay is reported to be 1.2 ng/L *(21)* and concentrations below 1.2 ng/L were assigned a value of 0.6 ng/L. cTnT was measured from September 2017 through March 2018 with the troponin T hs STAT assay (Roche Diagnostics). LoD for this assay is reported to be 3 ng/L *(22)* and concentrations below 3 ng/L were assigned a value of 1.5 ng/L. Concentrations of cTn at or above LoD were defined as measurable. Both biomarkers were measured in thawed serum samples, and coefficient of variation derived from manufacturer control material are outlined in Supplemental Table 2.

STATISTICAL METHODS

We report baseline data as absolute numbers (proportion) or median (interquartile range) unless otherwise stated. Continuous variables were analyzed with the Mann-Whitney U test, and categorical variables were analyzed with the Fisher exact test. Continuous concentrations of cTnI and cTnT were transformed by the natural logarithm prior to use in regression analyses due to right skewed distribution and to diminish the impact of outliers. We also categorized concentrations of cTn according to the upper sex specific quartiles of cTnI (≥1.8 ng/L for women and ≥3.5 ng/L for men) and cTnT (≥6.0 ng/L for women and ≥10.0 ng/L for men). From these groups we designated subjects to groups with concordant low concentrations (both cTnI and cTnT below the upper sex specific quartiles), discordant high concentrations (either cTnI or cTnT in the upper sex specific quartile), and concordant high concentrations (both cTnI and cTnT in the upper sex specific quartiles) of cTn. Correlations were assessed by Spearman rank correlation coefficients. Linear regression analyses were used to assess determinants of continuous cTn concentrations. Associations between echocardiographic variables and cTn concentrations were assessed both by linear and logistic regression. As previously suggested *(23)*, the logistic regression models were constructed on the lower sex specific deciles of GLS (<17.6% for women, <16.8% for men), and LVEF (<50% for women, <48.5% for men), and the upper sex specific decile of LVMI (>90.5 g/m^2 for women, >102.8 g/m^2 for men) from values derived from the study cohort, the latter constituting the presence of LV hypertrophy. All regression models were adjusted for sex, age, study site, and a priori selected variables influencing CV risk (body mass index [BMI], eGFR, total and HDL cholesterol, CRP, education, hypertension, diabetes mellitus, smoking status, and alcohol consumption). Adjustment was also made for current statin therapy, as statin therapy has been found associated with attenuated cTn concentrations *(24)*. The incremental value of biomarker concentrations to established CV risk factors was assessed by *c*-statistics derived from the logistic regression models, as well as by the net reclassification index (NRI) and integrated discrimination improvement (IDI) calculated by the R package "PredictABEL" *(25)*. The analyses were performed with IBM SPSS Statistics for Windows, version 25 (IBM Corp), STATA 15 (StataCorp LP), MedCalc for Windows, version 18.2.1 (MedCalc Software), and R 3.4.3 (R Foundation for Statistical Computing).

Results

BASELINE CHARACTERISTICS

Of the 3706 subjects from the ACE 1950 Study baseline examination, 1236 women and 1157 men were included in the following analyses (Fig. 1). Characteristics of subjects excluded due to history of CAD (n = 263 [7.1%]), or missing data for GLS (n = 1047 [28.3%]) or biomarker concentrations (n = 3 [0.1%]) are summarized in Supplemental Table 3. Briefly, excluded subjects were more frequently male with prevalent hypertension, obesity, and diabetes mellitus, and more frequently on cardioprotective and antidiabetic drug therapy. They additionally exhibited increased concentrations of cTnI and cTnT, and lower GLS and LVEF and higher LVMI.

Concentrations of cTnI were measurable in 60.3% and cTnT in 72.5% of study participants ($P < 0.001$), and were modestly correlated ($r = 0.53$; $P < 0.001$). Concentrations of cTnI were more strongly associated with male sex ($P = 0.018$ vs. cTnT), age ($P < 0.001$ vs. cTnT), higher education ($P < 0.001$ vs. cTnT), and history of hypertension ($P < 0.001$ vs. cTnT). cTnT was more strongly and inversely associated with eGFR ($P = 0.015$ vs. cTnI). Both cTnI and cTnT were similarly associated with BMI (P for comparison = 0.09)

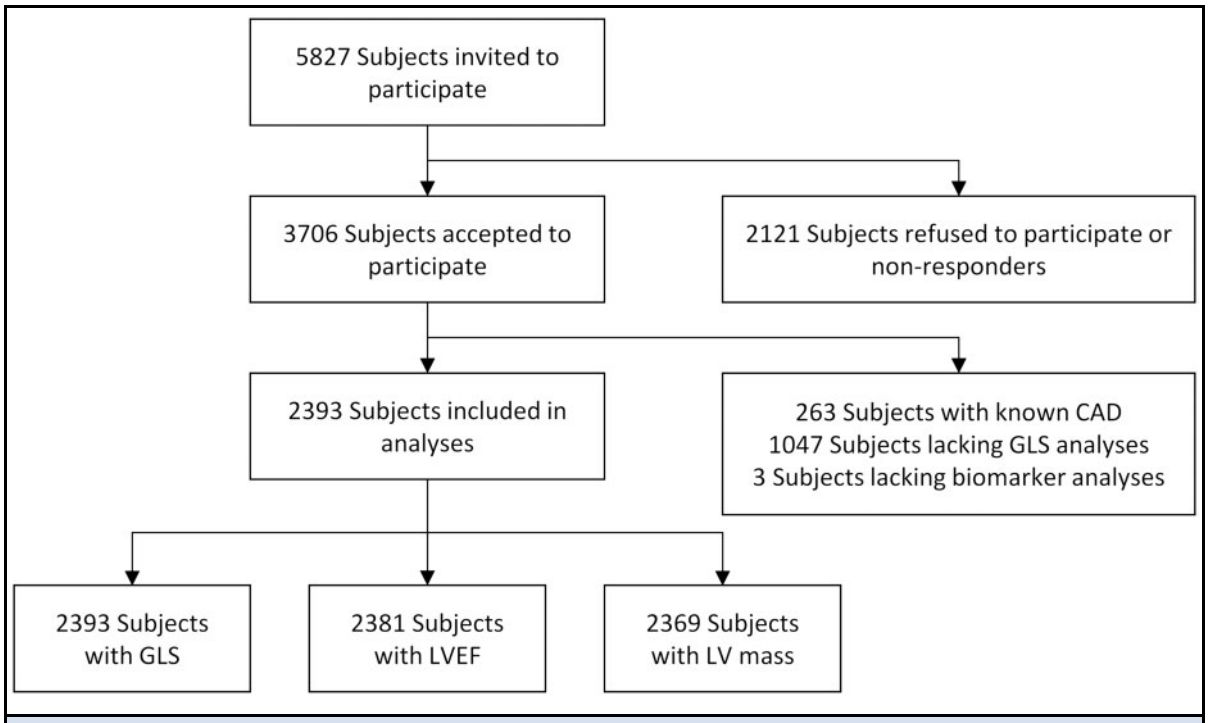

Fig. 1. Flow chart of participation in the study.

and HDL cholesterol (P for comparison = 0.15; Supplemental Table 4).

Study participants exhibiting concordant high concentrations of cTn, defined as being in the upper sex-specific quartiles of both cTnI and cTnT, were more frequently on cardioprotective drug therapy, had higher BMI and blood pressure, more prevalent hypertension and diabetes mellitus, and more frequently had higher education. They were less frequently current smokers and had lower eGFR. GLS was lower and LVMI higher in subjects with increased concentrations of both cTnI and cTnT, while no difference in LVEF was observed between groups (Table 1).

ASSOCIATIONS BETWEEN CARDIAC TROPONIN AND LEFT VENTRICULAR ECHOCARDIOGRAPHIC INDICES

Both cTnI and cTnT were positively correlated with LVMI, and negatively correlated with GLS and LVEF (Supplemental Table 5). The strongest correlations were those with LVMI (cTnI $r = 0.28$; $P < 0.001$, cTnT $r = 0.20$; $P < 0.001$). In analyses using echocardiographic measures as continuous outcomes, continuous concentrations of cTnI (B -0.17, 95% confidence interval [CI] -0.27 to -0.07) and cTnT (B -0.12, 95% CI -0.23 to -0.01) were similarly associated with GLS (P for comparison = 0.30). When adjusting for both cTnI and cTnT, the association of cTnT (B -0.04, 95% CI -0.16 to 0.09) with GLS was attenuated but remained significant for cTnI (B -0.16, 95% CI -0.27 to -0.04). No adjusted associations were present in analyses with LVEF. As for the correlation analyses, the strongest adjusted associations were those with LVMI. Both cTnI (B 3.12, 95% CI 2.44 to 3.81) and cTnT (B 1.98, 95% CI 1.21 to 2.75) were independently associated with continuous levels of LVMI, but stronger for cTnI (P for comparison = 0.035). Both cTnI (B 2.74, 95% CI 1.98 to 3.49) and cTnT (B 1.02, 95% CI 0.19 to 1.85) remained significant predictors of LVMI in analyses adjusting for both biomarkers. In models according to the lower sex-specific deciles of GLS and LVEF and the upper sex-specific decile of LVMI, we found comparable adjusted associations of cTnI (odds ratio [OR] 1.50, 95% CI 1.32 to 1.71) and cTnT (OR 1.45, 95% CI 1.24 to 1.70) with LV hypertrophy (P for comparison = 0.63). Both cTnI (OR 1.39, 95% CI 1.20 to 1.61) and cTnT (OR 1.22, 95% CI 1.02 to 1.46) remained significant predictors of LV hypertrophy in analyses adjusting for both biomarkers (Table 2).

Statistical models were also constructed according to concordant and discordant high concentrations of cTn. Using study subjects with concordant low concentrations of cTn as reference, subjects with concordant high concentrations of cTn exhibited the highest levels of LVMI, and subjects with high concentrations of

Table 1. Baseline characteristics according to sex-specific concentrations of cardiac troponin I and cardiac troponin T.

	Concordant low concentrations (cTnI and cTnT low)		Discordant high concentrations (cTnI or cTnT high)		Concordant high concentrations (cTnI and cTnT high)	
Variable	***n***	**Value**	***n***	**Value**	***n***	**Value**
Male sex, *n* (%)	1810	872 (48.2)	303	151 (49.8)	280	134 (47.9)
Age, years	1810	64.0 (63.5 to 64.5)	303	63.8 (63.4 to 64.5)	280	63.8 (63.4 to 64.5)
Higher education, *n* (%)	1803	835 (46.3)	303	144 (47.5)	279	153 (54.8)[b]
Current smoker, *n* (%)	1802	273 (15.1)	302	29 (9.6)[a]	277	22 (7.9)[b]
Alcohol consumption, units/2 weeks	1810	6 (2 to 10)	303	6 (2 to 12)	280	5 (2 to 10)
Study site Akershus University Hospital, *n* (%)	1810	1294 (71.5)	303	191 (63.9)[b]	280	176 (62.9)[b]
Clinical measurements						
Body mass index, kg/m^2	1810	25.9 (23.6 to 28.3)	303	26.8 (24.2 to 29.7)[c]	280	26.7 (24.2 to 29.6)[c]
Ventricular frequency, beats/min	1810	62 (56 to 68)	303	59 (54 to 67)[c]	279	60 (53 to 67)[c]
Systolic blood pressure, mmHg	1810	136 (124 to 147)	303	139 (127 to 154)[b]	280	142 (128 to 154)[c]
Diastolic blood pressure, mmHg	1810	76 (70 to 83)	303	77 (71 to 84)	280	78 (72 to 85)[b]
History of						
Hypertension, *n* (%)	1810	982 (54.3)	303	196 (64.7)[b]	280	199 (71.1)[c]
Chronic obstructive pulmonary disease, *n* (%)	1799	127 (7.1)	297	24 (8.1)	277	22 (7.9)
Diabetes mellitus, *n* (%)	1809	104 (5.7)	303	17 (5.6)	280	26 (9.3)[a]
Medication						
Antihypertensives, *n* (%)	1810	9 (0.5)	303	1 (0.3)	280	3 (1.1)
Diuretics, *n* (%)	1810	30 (1.7)	303	11 (3.6)[a]	280	13 (4.6)[b]
β blockers, *n* (%)	1810	125 (6.9)	303	38 (12.5)[b]	280	31 (11.1)[a]
Calcium antagonists, *n* (%)	1810	101 (5.6)	303	22 (7.3)	280	26 (9.3)[a]
ACE-I/ARB, *n* (%)	1810	370 (20.4)	303	78 (25.7)[a]	280	99 (35.4)[c]
Statins, *n* (%)	1810	351 (19.4)	303	72 (23.8)	280	68 (24.3)
Antidiabetics, *n* (%)	1810	63 (3.5)	303	11 (3.6)	280	13 (4.6)
Laboratory measurements						
Cardiac troponin I, ng/L	1810	0.6 (0.6 to 1.8)	303	2.9 (2.0 to 4.6)[c]	280	5.0 (3.6 to 9.2)[c]
Cardiac troponin T, ng/L	1810	5.0 (4.0 to 7.0)	303	8.0 (6.0 to 10.0)[c]	280	11.0 (8.0 to 14.0)[c]
Hemoglobin, g/dL	1807	14.2 (13.5 to 14.9)	303	14.3 (13.5 to 15.0)	279	14.3 (13.5 to 15.0)
White blood count, 10^9/L	1808	5.4 (4.5 to 6.4)	303	5.4 (4.6 to 6.3)	280	5.3 (4.5 to 6.4)
CRP, mg/L	1803	1.5 (1.5 to 1.5)	302	1.5 (1.5 to 1.5)	280	1.5 (1.5 to 1.5)
Glucose, mg/dL[d]	1807	95 (88 to 103)	301	94 (88 to 101)	280	95 (88 to 105)
HbA1c, %	1802	5.6 (5.4 to 5.9)	302	5.7 (5.4 to 5.9)	277	5.7 (5.4 to 6.0)
Total cholesterol, mg/dL[d]	1809	212 (185 to 239)	302	212 (185 to 236)	280	212 (185 to 239)
HDL cholesterol, mg/dL[d]	1808	58 (46 to 73)	302	58 (46 to 73)	280	58 (46 to 73)
Triglycerides, mg/dL[d]	1809	97 (71 to 142)	302	97 (71 to 133)	280	97 (80 to 142)
eGFR, mL/min/1.73 m^2	1802	85.5 (76.1 to 92.5)	302	83.6 (74.5 to 91.8)	279	80.3 (70.1 to 90.9)[c]
Echocardiographic measurements						
Global longitudinal strain, %	1810	20.4 (18.7 to 21.8)	303	20.0 (18.5 to 21.7)	280	19.8 (18.2 to 21.9)[a]
Left ventricular ejection fraction, %	1800	55.9 (52.3 to 59.4)	302	55.6 (52.3 to 59.3)	279	55.7 (52.4 to 59.0)
Left ventricular mass index, g/m^2	1795	72.4 (62.6 to 83.8)	300	75.7 (65.8 to 86.4)[c]	274	78.5 (67.4 to 93.4)[c]

High concentrations of cTn equaling sex-specific fourth quartile, low concentrations equaling sex-specific first to third quartile.
[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$ compared to subjects with low cTnI and low cTnT.
[d] To convert glucose concentrations from mg/dL to mmol/L, multiply by 0.05556. To convert triglyceride concentrations from mg/dL to mmol/L, multiply by 0.01129. To convert cholesterol concentrations from mg/dL to mmol/L, multiply by 0.02586.

Table 2. Associations between continuous cardiac troponin concentrations and indices of left ventricular structure and function.

		Model 1	Model 2	Model 3	Model 4
			Continuous[a]		
			B (95% CI)		
Global longitudinal strain (n=2393)	cTnI	−0.35 (-0.45 to -0.25)	−0.20 (-0.30 to -0.10)	−0.17 (-0.27 to -0.07)	−0.16 (-0.27 to -0.04)
	cTnT	−0.42 (-0.51 to -0.32)	−0.21 (-0.32 to -0.10)	−0.12 (-0.23 to -0.01)	−0.04 (-0.16 to 0.09)
Left ventricular ejection fraction (n=2381)	cTnI	−0.41 (-0.63 to -0.20)	−0.21 (-0.43 to 0.01)	−0.21 (-0.43 to 0.02)	−0.13 (-0.38 to 0.12)
	cTnT	−0.77 (-0.98 to -0.55)	−0.32 (-0.56 to -0.08)	−0.29 (-0.54 to -0.04)	−0.20 (-0.47 to 0.08)
Left ventricular mass index (n=2369)	cTnI	4.46 (3.80 to 5.13)	3.43 (2.76 to 4.11)	3.12 (2.44 to 3.81)	2.74 (1.98 to 3.49)
	cTnT	3.25 (2.58 to 3.93)	2.05 (1.30 to 2.79)	1.98 (1.21 to 2.75)	1.02 (0.19 to 1.85)
			Sex-specific cutoffs[b]		
			Odds ratio (95% CI)		
Global longitudinal strain (n=2393)	cTnI	1.16 (1.02 to 1.31)	1.19 (1.05 to 1.36)	1.15 (1.00 to 1.33)	1.13 (0.96 to 1.33)
	cTnT	1.17 (1.04 to 1.34)	1.25 (1.08 to 1.44)	1.12 (0.96 to 1.31)	1.05 (0.88 to 1.25)
Left ventricular ejection fraction (n=2381)	cTnI	1.03 (0.90 to 1.18)	1.08 (0.94 to 1.24)	1.04 (0.90 to 1.21)	1.02 (0.86 to 1.20)
	cTnT	1.06 (0.93 to 1.21)	1.12 (0.97 to 1.30)	1.07 (0.91 to 1.25)	1.06 (0.89 to 1.26)
Left ventricular mass index (n=2369)	cTnI	1.41 (1.25 to 1.59)	1.51 (1.33 to 1.72)	1.50 (1.32 to 1.71)	1.39 (1.20 to 1.61)
	cTnT	1.25 (1.09 to 1.42)	1.41 (1.22 to 1.63)	1.45 (1.24 to 1.70)	1.22 (1.02 to 1.46)

[a]Continuous echocardiographic values.
[b]Lower sex-specific decile of GLS and LVEF, upper sex-specific decile of LVMI. All coefficients reported per 1 SD increase in cTn concentration (transformed by the natural logarithm). Model 1, unadjusted. Model 2, adjusted for sex, age and study site. Model 3, adjusted for model 2, BMI, eGFR, total and HDL cholesterol, CRP, higher education, statin therapy, hypertension, diabetes mellitus, current smoking, and alcohol consumption. Model 4, adjusted for model 3 and both cTnI and cTnT.

either biomarker exhibited in-between levels of LVMI (Fig. 2; Table 3). We observed no significant associations with GLS or LVEF in these models.

DISCRIMINATION AND RECLASSIFICATION

We constructed discrimination and reclassification models identifying subjects with decreased GLS and LVEF, and increased LVMI (i.e., LV hypertrophy), using both continuous cTn concentrations and dichotomized according to sex-specific quartiles of cTn (subjects with both cTnI and cTnT in the upper sex-specific quartile vs. the rest). Overall, significant improvements in discrimination and reclassification for LV hypertrophy were observed when cTnI and cTnT were added to established CV risk factors. The improvements were however superior in the models constructed on concentrations of cTnI. We observed no further improvements in model prediction when cTnT was added to models constructed on established CV risk factors and cTnI. Prediction models using continuous concentrations of cTnI outperformed prediction models using cTn dichotomized according to concordant high concentrations. No significant improvements were demonstrated in any models for GLS or LVEF, apart from minor improvements in IDI for cTnI predicting GLS (Table 4).

Discussion

In a large community-based study with quantification of cTnI and cTnT, we demonstrate that both cTnI and cTnT are independently associated with LVMI and that subjects with concomitant high cTnI and cTnT concentration exhibit the highest levels of LVMI. When added to conventional CV risk factors, cTnI provides robust improvements in discrimination and reclassification models for LV hypertrophy. The addition of cTnT did however not improve model prediction further.

In patients with acute myocardial infarction, concentrations of cTnI and cTnT are highly correlated *(26, 27)* and are interchangeable in diagnosing significant myocardial necrosis. Conversely, in the chronic setting, concentrations of cTnI and cTnT are only moderately correlated ($r = 0.5 \pm 0.1$) *(15, 16, 28)*, which is in accordance with observations made in the current investigation. Additionally, common CV risk factors differentially influenced continuous concentrations of cTnI and cTnT. Male sex and history of hypertension, two of the strongest risk factors for incident CV disease, were more strongly associated with concentrations of cTnI. Similar associations were recently demonstrated in the Scotland Scottish Family Health Study, where both systolic blood pressure and use of antihypertensives were more strongly associated with concentrations of cTnI *(14)*.

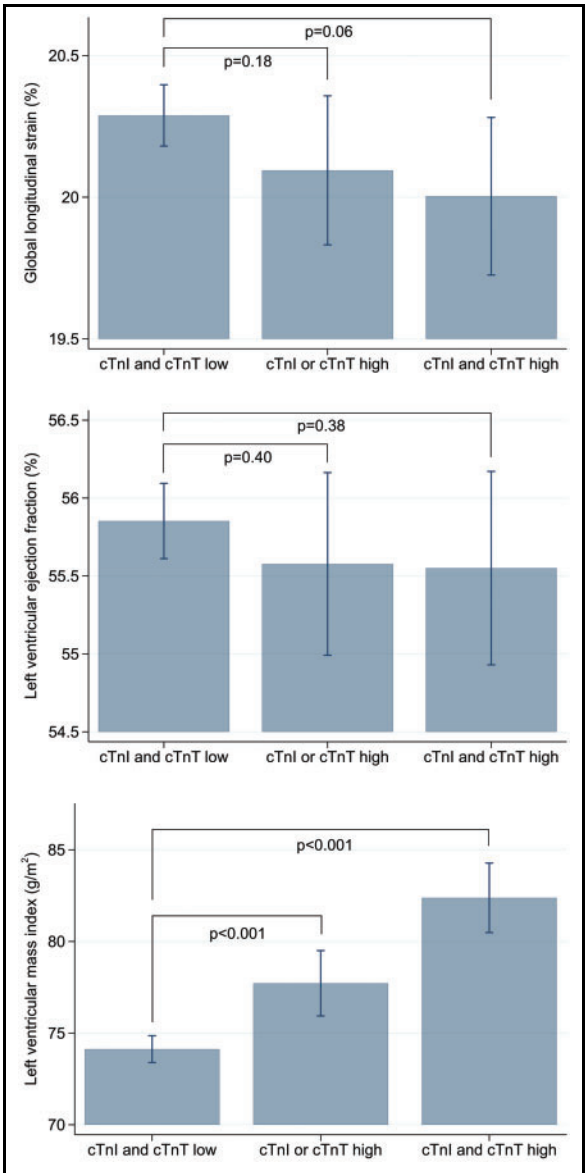

Fig. 2. Levels of global longitudinal strain, left ventricular ejection fraction, and left ventricular mass index in subjects with concordant low concentrations of cardiac troponin, discordant high concentrations of cardiac troponin, and concordant high concentrations of cardiac troponin (adjusted for sex, age, study site, BMI, eGFR, total and HDL cholesterol, CRP, higher education, statin therapy, hypertension, diabetes mellitus, current smoking, and alcohol consumption).

With regard to cTnT, renal function was more strongly associated with concentrations of cTnT. This is in accordance with previous literature, and mechanisms for this discrepancy with concentrations of cTnI remain unresolved. Several mechanisms have been proposed,

Table 3. Associations between concordant and discordant cardiac troponin concentrations and indices of left ventricular structure and function.

		Model 1	Model 2	Model 3
			Continuous[a]	
			B (95% CI)	
Global longitudinal strain (*n*=2393)	cTnI and cTnT low	Reference	Reference	Reference
	cTnI or cTnT high	−0.27 (-0.56 to 0.03)	−0.28 (-0.57 to 0.01)	−0.19 (-0.48 to 0.09)
	cTnI and cTnT high	−0.40 (-0.71 to -0.09)	−0.43 (-0.73 to -0.13)	−0.29 (-0.59 to 0.01)
Left ventricular ejection fraction (*n*=2381)	cTnI and cTnT low	Reference	Reference	Reference
	cTnI or cTnT high	−0.30 (-0.95 to 0.36)	−0.22 (-0.85 to 0.41)	−0.27 (-0.91 to 0.37)
	cTnI and cTnT high	−0.41 (-1.09 to 0.27)	−0.35 (-1.01 to 0.30)	−0.31 (-0.98 to 0.36)
Left ventricular mass index (*n*=2369)	cTnI and cTnT low	Reference	Reference	Reference
	cTnI or cTnT high	3.53 (1.46 to 5.59)	4.12 (2.18 to 6.06)	3.59 (1.66 to 5.53)
	cTnI and cTnT high	7.99 (5.84 to 10.14)	8.68 (6.66 to 10.69)	8.26 (6.21 to 10.30)
			Sex-specific cutoffs[b]	
			Odds ratio (95% CI)	
Global longitudinal strain (*n*=2393)	cTnI and cTnT low	Reference	Reference	Reference
	cTnI or cTnT high	1.32 (0.90 to 1.93)	1.36 (0.93 to 2.00)	1.21 (0.81 to 1.81)
	cTnI and cTnT high	1.31 (0.88 to 1.94)	1.35 (0.90 to 2.00)	1.12 (0.73 to 1.71)
Left ventricular ejection fraction (*n*=2381)	cTnI and cTnT low	Reference	Reference	Reference
	cTnI or cTnT high	0.99 (0.66 to 1.48)	1.05 (0.70 to 1.60)	1.00 (0.65 to 1.53)
	cTnI and cTnT high	0.96 (0.63 to 1.47)	1.01 (0.65 to 1.55)	0.92 (0.58 to 1.44)
Left ventricular mass index (*n*=2369)	cTnI and cTnT low	Reference	Reference	Reference
	cTnI or cTnT high	1.64 (1.11 to 2.41)	1.80 (1.22 to 2.66)	1.84 (1.23 to 2.75)
	cTnI and cTnT high	3.06 (2.18 to 4.29)	3.41 (2.41 to 4.82)	3.57 (2.48 to 5.15)

[a]Continuous echocardiographic values.
[b]Lower sex-specific decile of GLS and LVEF, upper sex-specific decile of LVMI. High concentrations of cTn equaling sex-specific fourth quartile, low concentrations equaling sex-specific first to third quartile. Model 1, unadjusted. Model 2, adjusted for sex, age, and study site. Model 3, adjusted for model 2, BMI, eGFR, total and HDL cholesterol, CRP, higher education, statin therapy, hypertension, diabetes mellitus, current smoking, and alcohol consumption.

Table 4. Diagnostic performance of cardiac troponins on GLS, LVEF, and LVMI.

Model	GLS	LVEF	LVMI
		C-statistics (95% CI)	
Risk factors	0.663 (0.644 to 0.682)	0.700 (0.681 to 0.718)	0.626 (0.606 to 0.646)
Risk factors + cTnI	0.664 (0.644 to 0.683; P=0.91[a])	0.701 (0.682 to 0.719; P=0.39[a])	0.673 (0.653 to 0.692; P<0.001[a])
Risk factors + cTnT	0.667 (0.648 to 0.686; P=0.24[a])	0.701 (0.682 to 0.720; P=0.36[a])	0.645 (0.625 to 0.664; P=0.04[a])
Risk factors + cTnI + cTnT	0.666 (0.646 to 0.685; P=0.28[b])	0.701 (0.682 to 0.719; P=0.98[b])	0.675 (0.655 to 0.694; P=0.45[b])
Risk factors + high cTnI and cTnT[c]	0.663 (0.643 to 0.682; P=0.72[a])	0.699 (0.680 to 0.718; P=0.75[a])	0.668 (0.649 to 0.687; P=0.002[a])
		Net Reclassification Index (95% CI)	
Risk factors + cTnI	0.107 (-0.030 to 0.243; P=0.13[a])	−0.053 (-0.187 to 0.080; P=0.43[a])	0.422 (0.287 to 0.556; P<0.001[a])
Risk factors + cTnT	0.065 (-0.071 to 0.202; P=0.35[a])	−0.013 (-0.148 to 0.122; P=0.85[a])	0.204 (0.069 to 0.340; P=0.003[a])
Risk factors + cTnI + cTnT	0.038 (-0.097 to 0.174; P=0.58[b])	0.022 (-0.112 to 0.156; P=0.75[b])	0.070 (-0.065 to 0.205; P=0.31[b])
Risk factors + high cTnI and cTnT[c]	0.037 (-0.069 to 0.142; P=0.50[a])	0.033 (-0.064 to 0.130; P=0.50[a])	0.238 (0.124 to 0.353; P<0.001[a])
		Integrated Discrimination Improvement (95% CI)	
Risk factors + cTnI	0.0026 (0.0003 to 0.0048; P=0.025[a])	0.0002 (-0.0005 to 0.0008; P=0.61[a])	0.0158 (0.0089 to 0.0226; P<0.001[a])
Risk factors + cTnT	0.0010 (-0.0007 to 0.0027; P=0.25[a])	0.0003 (-0.0004 to 0.0010; P=0.33[a])	0.0057 (0.0017 to 0.0098; P=0.005[a])
Risk factors + cTnI + cTnT	0 (-0.0008 to 0.0008; P=0.97[b])	0.0002 (-0.0003 to 0.0006; P=0.44[b])	0.0009 (-0.0003 to 0.0020; P=0.16[b])
Risk factors + high cTnI and cTnT[c]	0.0004 (-0.0005 to 0.0012; P=0.41[a])	0.0002 (-0.0004 to 0.0007; P=0.51[a])	0.0174 (0.0097 to 0.0251; P<0.001[a])

[a]Compared to risk factor model (sex, age, BMI, eGFR, total and HDL cholesterol, CRP, higher education, hypertension, diabetes mellitus, current smoking, and alcohol consumption).
[b]Compared to risk factor model + cTnI.
[c]Subjects with both cTnI and cTnT in the upper sex-specific quartile vs rest.

including differences in protein binding of circulating free cTn and differences in assay specificity. cTnI may additionally be more susceptible to chemical modifications that may alter protein concentrations *(29)*. Even though subjects with established CAD were excluded from the current investigation, we cannot rule out the possibility that small increases in cTn may partly be explained by subclinical coronary artery disease *(30)*.

LV mass is strongly associated with incident cardiovascular disease *(31)*, and attenuation of LV hypertrophy is paralleled by reductions in CV risk *(32, 33)*. In patients with hypertrophic cardiomyopathy *(34)* and severe aortic stenosis *(35)*, LV mass increases with increasing concentrations of cTnT. Similar associations have been demonstrated in the general population *(10)*. Concentrations of cTnI have likewise been associated with LV mass, both in the general population *(12)* and in patients with hypertrophic cardiomyopathy *(36)*. In the current study, we demonstrate strong associations of concentrations of cTnI and cTnT with LVMI, associations previously demonstrated for LV hypertrophy *(10, 37)*. We elaborate on these previous findings by demonstrating significant improvements in diagnostic models for assessing LV hypertrophy. Interestingly, the associations with LVMI were stronger for cTnI, and cTnT provided no additional information to established CV risk factors and cTnI in predicting LV hypertrophy. Male sex and hypertension are strong predictors of LV hypertrophy, and both were more strongly associated with concentrations of cTnI. These associations may indeed explain the superior association of cTnI with subclinical LV hypertrophy in our study.

cTn is a reliable indicator of myocardial injury and is associated with CV risk, both in presumably healthy community dwellers and in patients with established CV disease. Analogously to the prognostic information conveyed by cTn, GLS by echocardiography is one of the most sensitive investigations of LV systolic function *(8)*. Evidence is growing for the use of these tools in predicting unfavorable outcomes such as heart failure, acute myocardial infarction, and CV death *(9, 38, 39)*. To our knowledge, our study is the first to document significant associations between cTn and this highly sensitive index of LV systolic function.

We evaluated two important estimates of LV function in the current study, GLS and LVEF. In subjects recruited from the general population, concentrations of cTn are inversely associated with LVEF *(10, 11),* and subjects with lower LVEF are more likely to have increasing concentrations of cTnI over time *(12)*. We demonstrate inverse associations of both cTnI and cTnT with GLS, but no associations with LVEF. The reasons for this inconsistency may be several. LVEF is a crude measure of LV function among others suffering from poor reproducibility and inter-observer variability *(8)*. An increase in cTn is, on the other hand, a very sensitive index of subclinical myocardial injury preceding overt clinical disease such as heart failure by years. This discrepancy in sensitivity may very well explain the lack of any significant relationship between these two analyses. The significant association between cTnI and cTnT and GLS supports the sentiment that comparable sensitivity is a crucial trait when assessing relationships between different indices of subclinical CV disease.

In primary prevention, overall CV risk is commonly estimated by a combination of established CV risk factors such as age, sex, blood pressure, blood cholesterol, and smoking status. Several risk-enhancing factors such as diabetes mellitus, chronic kidney disease, and autoimmune disorders may additionally augment CV risk *(40)*. In the current study, we demonstrate strong diagnostic properties of cTn, especially in predicting subclinical LV hypertrophy, independently of established CV risk factors. Considering the consistent association of cTn with CV risk *(4, 5)*, increased concentrations of cTn within the normal range should be considered as well a risk-enhancing factor, possibly triggering early risk factor intervention and control. More specifically, this pertains to interventions aimed at reducing key modifiable CV risk factors (i.e., hypertension, diabetes mellitus/obesity, tobacco smoking, and blood cholesterol), all associated with the development of LV hypertrophy and ultimately overt CV disease. One of the strongest risk factors for the development of LV hypertrophy is indeed hypertension. In patients with hypertension, the presence of comorbidities like diabetes mellitus and chronic kidney disease may justify a more aggressive blood pressure target. Similar reasoning should be applied to hypertensive patients exhibiting low-grade increases in cTn within the normal range. Further supporting the sentiment of risk-enhancement by cTn, serial measurement of cTn may provide information on the effect of medical therapy aimed at reducing CV risk *(24)*, analogously to measurements of blood pressure, blood cholesterol, and HbA1c in contemporary clinical practice.

Several strengths and limitations of the current study merit mentioning. A major strength of the study is concomitant analyses of both cTnI and cTnT, allowing comparative analyses of the most frequently used contemporary cTn assays. Additionally, we performed an extensive and highly sensitive echocardiographic evaluation of LV function and structure. We have used data from a large community-based cohort with broad phenotypical characterization, as well as thorough registration of socioeconomic status and medical history. The data are, however, based on self-report and run the inevitable risk of response bias. Non-response bias must also be taken into account, as we did not have information on subjects who actively refused to participate or were

otherwise inaccessible for study inclusion. Finally, due to stringent exclusion criteria for the GLS analyses, a large proportion of the total study population was excluded from the statistical analyses. For that reason, the results cannot be generalized to the entire study cohort.

In conclusion, in a large community-based cohort examined with extensive echocardiography, concentrations of both cTnI and cTnT are associated with subclinical LV hypertrophy and dysfunction. Concentrations of cTnI do however appear superior to cTnT in predicting subclinical LV hypertrophy.

Supplemental Material

Supplemental material is available at *Clinical Chemistry* online.

Nonstandard Abbreviations: ACE, Akershus Cardiac Examination; ACE-I, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; cTn, cardiac troponin; cTnI, cardiac troponin I; cTnT, cardiac troponin T; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GLS, global longitudinal strain; HbA1c, glycated hemoglobin; HR, hazard ratio; IDI, integrated discrimination improvement; IQR, interquartile range; LoD, limit of detection; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NRI, net reclassification index.

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References

1. Gore MO, Seliger SL, Defilippi CR, Nambi V, Christenson RH, Hashim IA, et al. Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. J Am Coll Cardiol 2014;63:1441–8.
2. Everett BM, Cook NR, Magnone MC, Bobadilla M, Kim E, Rifai N, et al. Sensitive cardiac troponin T assay and the risk of incident cardiovascular disease in women with and without diabetes mellitus: The Women's Health Study. Circulation 2011;123:2811–8.
3. Apple FS, Murakami MM, Pearce LA, Herzog CA. Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. Circulation 2002;106:2941–5.
4. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the atherosclerosis risk in communities study. Circulation 2011;123:1367–76.
5. Zeller T, Tunstall-Pedoe H, Saarela O, Ojeda F, Schnabel RB, Tuovinen T, et al. High population prevalence of cardiac troponin I measured by a high-sensitivity assay and cardiovascular risk estimation: The MORGAM Biomarker Project Scottish Cohort. Eur Heart J 2014;35:271–81.
6. Hijazi Z, Siegbahn A, Andersson U, Granger CB, Alexander JH, Atar D, et al. High-sensitivity troponin I for risk assessment in patients with atrial fibrillation: insights from the Apixaban For Reduction In Stroke and Other Thromboembolic Events In Atrial Fibrillation (ARISTOTLE) trial. Circulation 2014;129:625–34.
7. Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J 2016;37:1196–207.
8. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart 2014;100:1673–80.
9. Biering-Sorensen T, Biering-Sorensen SR, Olsen FJ, Sengelov M, Jorgensen PG, Mogelvang R, et al. Global longitudinal strain by echocardiography predicts long-term risk of cardiovascular morbidity and mortality in a low-risk general population: The Copenhagen City Heart Study. Circ Cardiovasc Imaging 2017;10:e005521.
10. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010;304:2503–12.
11. Eggers KM, Johnston N, Lind L, Venge P, Lindahl B. Cardiac troponin I levels in an elderly population from the community-the implications of sex. Clin Biochem 2015;48:751–6.
12. Eggers KM, Venge P, Lindahl B, Lind L. Cardiac troponin I levels measured with a high-sensitive assay increase over time and are strong predictors of mortality in an elderly population. J Am Coll Cardiol 2013;61:1906–13.
13. Klinkenberg LJ, Wildi K, van der Linden N, Kouw IW, Niens M, Twerenbold R, et al. Diurnal rhythm of cardiac troponin: consequences for the diagnosis of acute myocardial infarction. Clin Chem 2016;62:1602–11.
14. Welsh P, Preiss D, Shah ASV, McAllister D, Briggs A, Boachie C, et al. Comparison between high-sensitivity cardiac troponin T and cardiac troponin I in a large general population cohort. Clin Chem 2018;64:1607–16.
15. Welsh P, Preiss D, Hayward C, Shah ASV, McAllister D, Briggs A, et al. Cardiac troponin T and troponin I in the general population. Circulation 2019;139:2754–64.
16. Jia X, Sun W, Hoogeveen RC, Nambi V, Matsushita K, Folsom AR, et al. High-sensitivity troponin I and incident coronary events, stroke, heart failure hospitalization, and mortality in the ARIC study. Circulation 2019;139:2642–53.
17. Berge T, Vigen T, Pervez MO, Ihle-Hansen H, Lyngbakken MN, Omland T, et al. Heart and brain interactions–The Akershus Cardiac Examination (ACE) 1950 Study design. Scand Cardiovasc J 2015;49:308–15.
18. Aagaard EN, Kvisvik B, Pervez MO, Lyngbakken MN, Berge T, Enger S, et al. Left ventricular mechanical dispersion in a general population: data from the Akershus Cardiac Examination 1950 Study. Eur Heart J Cardiovasc Imaging 2020;21:183–190.
19. Voigt J-U, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2d speckle tracking echocardiography: consensus

document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2015;16:1–11.
20. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317:1098.
21. Apple FS, Collinson PO; IFCC Task Force on Clinical Applications of Cardiac Biomarkers. Analytical characteristics of high-sensitivity cardiac troponin assays. Clin Chem 2012;58:54–61.
22. Sandoval Y, Jaffe AS. Using high-sensitivity cardiac troponin T for acute cardiac care. Am J Med 2017;130:1358–65 e1.
23. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PWF, Levy D. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction the Framingham Heart Study. JAMA 2002;288:1252–9.
24. Ford I, Shah AS, Zhang R, McAllister DA, Strachan FE, Caslake M, et al. High-sensitivity cardiac troponin, statin therapy, and risk of coronary heart disease. J Am Coll Cardiol 2016;68:2719–28.
25. Kundu S, Aulchenko YS, van Duijn CM, Janssens AC. Predictabel: an R package for the assessment of risk prediction models. Eur J Epidemiol 2011;26:261–4.
26. Haaf P, Reichlin T, Twerenbold R, Hoeller R, Rubini Gimenez M, Zellweger C, et al. Risk stratification in patients with acute chest pain using three high-sensitivity cardiac troponin assays. Eur Heart J 2014;35:365–75.
27. Kvisvik B, Morkrid L, Rosjo H, Cvancarova M, Rowe AD, Eek C, et al. High-sensitivity troponin T vs I in acute coronary syndrome: prediction of significant coronary lesions and long-term prognosis. Clin Chem 2017;63:552–62.
28. Kimenai DM, Martens RJH, Kooman JP, Stehouwer CDA, Tan FES, Schaper NC, et al. Troponin I and T in relation to cardiac injury detected with electrocardiography in a population-based cohort - The Maastricht Study. Sci Rep 2017;7:6610.
29. Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. J Am Coll Cardiol 2002;40:2065–71.
30. Skadberg O, Kleiven O, Bjorkavoll-Bergseth M, Melberg T, Bergseth R, Selvag J, et al. Highly increased troponin I levels following high-intensity endurance cycling may detect subclinical coronary artery disease in presumably healthy leisure sport cyclists: The North Sea Race Endurance Exercise Study (NEEDED) 2013. Eur J Prev Cardiolog 2017;24:885–94.
31. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Left ventricular mass and incidence of coronary heart disease in an elderly cohort. The Framingham Heart Study. Ann Intern Med 1989;110:101–7.
32. Hatani T, Kitai T, Murai R, Kim K, Ehara N, Kobori A, et al. Associations of residual left ventricular and left atrial remodeling with clinical outcomes in patients after aortic valve replacement for severe aortic stenosis. J Cardiol 2016;68:241–7.
33. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I, et al. Prognostic significance of serial changes in left ventricular mass in essential hypertension. Circulation 1998;97:48–54.
34. Kubo T, Kitaoka H, Yamanaka S, Hirota T, Baba Y, Hayashi K, et al. Significance of high-sensitivity cardiac troponin T in hypertrophic cardiomyopathy. J Am Coll Cardiol 2013;62:1252–9.
35. Rosjo H, Andreassen J, Edvardsen T, Omland T. Prognostic usefulness of circulating high-sensitivity troponin T in aortic stenosis and relation to echocardiographic indexes of cardiac function and anatomy. Am J Cardiol 2011;108:88–91.
36. Kubo T, Kitaoka H, Okawa M, Yamanaka S, Hirota T, Hoshikawa E, et al. Serum cardiac troponin I is related to increased left ventricular wall thickness, left ventricular dysfunction, and male gender in hypertrophic cardiomyopathy. Clin Cardiol 2010;33:E1–7.
37. Myhre PL, O'Meara E, Claggett BL, de Denus S, Jarolim P, Anand IS, et al. Cardiac troponin I and risk of cardiac events in patients with heart failure and preserved ejection fraction. Circ Heart Fail 2018;11:e005312.
38. Willeit P, Welsh P, Evans JDW, Tschiderer L, Boachie C, Jukema JW, et al. High-sensitivity cardiac troponin concentration and risk of first-ever cardiovascular outcomes in 154,052 participants. J Am Coll Cardiol 2017;70:558–68.
39. Evans JDW, Dobbin SJH, Pettit SJ, Di Angelantonio E, Willeit P. High-sensitivity cardiac troponin and new-onset heart failure: a systematic review and meta-analysis of 67,063 patients with 4,165 incident heart failure events. JACC Heart Fail 2018;6:187–97.
40. Lloyd-Jones DM, Braun LT, Ndumele CE, Smith SC Jr, Sperling LS, Virani SS, Blumenthal RS. Use of risk assessment tools to guide decision-making in the primary prevention of atherosclerotic cardiovascular disease: a special report from the American Heart Association and American College of Cardiology. Circulation 2019;139:e1162–e77.