

LESS IS MORE

High-Sensitivity Cardiac Troponin T Levels and Secondary Events in Outpatients With Coronary Heart Disease From the Heart and Soul Study

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Importance: Levels of high-sensitivity cardiac troponin T (hs-cTnT) predict secondary cardiovascular events in patients with stable coronary heart disease.

Objectives: To determine the association of hs-cTnT levels with structural and functional measures of heart disease and the extent to which these measures explain the relationship between hs-cTnT and secondary events.

Design: We measured serum concentrations of hs-cTnT and performed exercise treadmill testing with stress echocardiography in a prospective cohort study of outpatients with coronary heart disease who were enrolled from September 11, 2000, through December 20, 2002, and followed up for a median of 8.2 years.

Setting: Twelve outpatient clinics in the San Francisco Bay Area.

Participants: Nine hundred eighty-four patients with stable coronary heart disease.

Main Outcomes and Measures: Cardiovascular events (myocardial infarction, heart failure, or cardiovascular death), determined by review of medical records and death certificates.

Results: Of 984 participants, 794 (80.7%) had detectable hs-cTnT levels. At baseline, higher hs-cTnT levels were associated with greater inducible ischemia and worse left ventricular ejection fraction, left atrial function, diastolic function, left ventricular mass, and treadmill exercise capacity. During follow-up, 317 participants (32.2%) experienced a cardiovascular event. After adjustment for clinical risk factors, baseline cardiac structure and function, and other biomarkers (N-terminal portion of the prohormone of brain-type natriuretic peptide and C-reactive protein levels), each doubling in hs-cTnT level remained associated with a 37% higher rate of cardiovascular events (hazard ratio, 1.37 [95% CI, 1.14-1.65]; $P = .001$).

Conclusions and Relevance: In outpatients with stable coronary heart disease, higher hs-cTnT levels were associated with multiple abnormalities of cardiac structure and function but remained independently predictive of secondary events. These findings suggest that hs-cTnT levels may detect an element of risk that is not captured by existing measures of cardiac disease severity.

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STANDARD SERUM CARDIAC troponin assays can detect measurable levels of troponin in the setting of myocardial injury,¹ but most healthy individuals and ambulatory patients with coronary heart disease (CHD) have undetectable levels.² Recently, high-sensitivity assays have been developed that can detect cardiac troponin levels in most healthy individuals.³

In the general population, levels of troponin within the range detected by high-sensitivity assays are associated with structural heart disease.⁴ In patients with stable CHD, elevated levels of high-sensitivity cardiac troponin T (hs-cTnT) predict a greater risk of secondary events.⁵ How-

ever, whether the increased risk of secondary events associated with elevated hs-cTnT levels is independent of existing measures of cardiac structural and functional abnormalities remains unclear.

See Editor's Note at end of article

Therefore, we sought to evaluate the association of hs-cTnT levels with baseline measures of cardiac structure and function and to determine whether the association of hs-cTnT levels with cardiovascular events was explained by baseline cardiac structure and function in a prospective cohort study of 984 outpatients with CHD.

PARTICIPANTS

We included for evaluation 984 patients from the Heart and Soul Study, a prospective cohort study originally designed to investigate the effects of psychosocial factors on outcomes in outpatients with stable CHD. Methods have been previously described.⁶ Patients were eligible if they had at least 1 of the following: history of myocardial infarction, angiographic evidence of at least 50% stenosis in at least 1 coronary vessel, evidence of exercise-induced ischemia by treadmill electrocardiography or stress nuclear perfusion imaging, or a history of coronary revascularization. Patients were excluded if they were unable to walk 1 block, had an acute coronary syndrome within the previous 6 months, or were likely to move out of the area within 3 years.

From September 11, 2000, through December 20, 2002, 1024 subjects were enrolled from 12 outpatient clinics in the San Francisco Bay Area, including 549 (53.6%) with a history of myocardial infarction, 237 (23.1%) with a history of revascularization but not myocardial infarction, and 238 (23.2%) with a diagnosis of coronary disease documented by their physician based on a positive angiogram or treadmill test result in more than 98% of cases. All study participants completed a full-day study, including medical history, questionnaires, and an exercise treadmill test with baseline and stress echocardiograms. Twelve-hour fasting serum samples were obtained on the morning before the stress test. The samples were centrifuged, divided into aliquots, and frozen at -80°C within 60 minutes of the blood draw. Samples underwent 2 freeze-thaw cycles before the hs-cTnT assays in October of 2012. Frozen samples were not available for 36 participants, and 4 were lost to follow-up, leaving 984 subjects for this analysis.

hs-cTnT ASSAY

Cardiac troponin T concentrations were measured with highly sensitive reagents on a commercially available analyzer (Elecscys 2010; Roche Diagnostics). The analytical measurement range of the assay was 3 to 10 000 pg/mL (to convert troponin T concentrations to micrograms per liter, multiply by 0.001). The limit of blank was 3 pg/mL; the limit of detection, 5 pg/mL. Values below the limit of detection were analyzed as 4.99 pg/mL. In validation studies of hs-cTnT, the 99th percentile for a healthy reference population has been reported to be 13.5 (10.0 in women and 14.5 in men) pg/mL⁷ and 14.5 pg/mL,⁸ with a coefficient of variation at or near 10% at the 99th percentile levels.^{7,8}

OUTCOMES ASCERTAINMENT

Annual telephone interviews were conducted with participants or their proxy to inquire about interval emergency department visits, hospitalizations, or death. For any reported event, medical records, electrocardiograms, death certificates, autopsy reports, and coroner's reports were obtained. Each event was adjudicated by 2 independent and blinded reviewers. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator, if needed.

The primary outcome was time to secondary cardiovascular event (myocardial infarction, heart failure, or cardiovascular death). Myocardial infarction was defined using standard diagnostic criteria.⁹ Heart failure was defined as hospitalization for signs and symptoms of heart failure. Death and cause of death were verified by death certificates and review of medical records.

OTHER PATIENT CHARACTERISTICS

Demographic characteristics, medical history, and smoking status were collected with a self-report questionnaire. Depressive symptoms were assessed using the 9-item Patient Health Questionnaire, a self-report instrument that measures the frequency of depressive symptoms, with a score of 10 or higher being classified as having depressive symptoms.¹⁰ We measured weight and height and calculated the body mass index as weight in kilograms divided by height in meters squared. Resting blood pressure was measured in the supine position with a standard sphygmomanometer. Participants were asked to bring their medication bottles to the study appointment, and research personnel recorded all current medications. Medications were categorized using a software application (Epocrates Rx; Epocrates Inc).

Levels of total cholesterol, high-density lipoprotein cholesterol, the N-terminal portion of the prohormone of brain-type natriuretic peptide (NT-proBNP) (Elecscys proBNP immunoassay; Roche Diagnostics), high-sensitivity C-reactive protein, and standard cardiac troponin T (Elecscys TnT third-generation assay; Roche Diagnostics) were determined from 12-hour fasting serum samples. Estimated glomerular filtration rate (eGFR) was calculated from levels of creatinine and cystatin C.¹¹

MEASURES OF CARDIAC STRUCTURE AND FUNCTION

Participants underwent symptom-limited exercise stress testing according to a standard Bruce protocol (those unable to complete the standard protocol underwent conversion to a manual protocol) with continuous 12-lead electrocardiographic monitoring. Exercise capacity was estimated as the total metabolic equivalents achieved at peak exercise.¹² Before exercise, participants underwent complete resting 2-dimensional echocardiography with all standard views using an ultrasound system (Acuson Sequoia; Siemens Medical Solutions) with a 3.5-MHz transducer and Doppler ultrasonographic examination. Standard 2-dimensional parasternal short-axis and apical 2- and 4-chamber views were obtained during held inspiration and were used to calculate chamber sizes and left ventricular ejection fraction.¹³ Chamber size measurements were indexed to body surface area. Using pulse-wave Doppler imaging, we measured the velocity time integral of the left ventricular outflow tract from the apical 5-chamber view. Left atrial function index was calculated using the formula [(left atrial emptying fraction \times left ventricular outflow tract-velocity time integral)/left atrial end-systolic volume index], where left atrial emptying fraction was defined as the difference between the left atrial end systolic volume and the left atrial end-diastolic volume divided by the left atrial end-systolic volume.¹⁴ Diastolic dysfunction was defined as pseudonormal or restrictive filling on mitral inflow.⁶ At peak exercise, precordial long- and short-axis and apical 2- and 4-chamber views were obtained to ascertain wall motion abnormalities. We defined exercise-induced ischemia as the presence of 1 or more new wall motion abnormalities at peak exercise that were not present at rest. A single experienced cardiologist (N.B.S.) who was blinded to the results of hs-cTnT level measurement and clinical histories interpreted all echocardiograms.

STATISTICAL ANALYSIS

For descriptive purposes, we divided participants into tertiles of hs-cTnT levels. To compare the differences among tertiles, we used the χ^2 test for categorical variables and 1-way analysis of variance for continuous variables.

For the primary combined outcome of myocardial infarction, heart failure, or cardiovascular death, we constructed Kaplan-Meier curves for event-free survival by tertile of hs-cTnT level and compared groups using the log-rank test. We calculated event rates per 100 person-years by category of hs-cTnT level for myocardial infarction, heart failure, cardiovascular death, and the primary combined outcome. Event rates by category were compared with the Mantel-Haenszel test for trend and Cox proportional hazards regression models.

To evaluate the possibility that the association between cardiac troponin T and cardiovascular events was due to categorization, we analyzed hs-cTnT levels as a continuous variable. We used Cox proportional hazards regression models to evaluate the association of each doubling in hs-cTnT level (base-2 logarithm-transformed hs-cTnT) with secondary cardiovascular events. We adjusted for clinical risk factors, stress echocardiographic measures, and cardiac biomarkers found to be associated with hs-cTnT at a level of $P < .10$. We tested for interactions of hs-cTnT level, age, sex, smoking, diabetes mellitus, eGFR, left ventricular ejection fraction, and left ventricular mass in predicting cardiovascular events. Finally, we evaluated the association between sex-specific tertiles of hs-cTnT levels and cardiovascular events.

Using a logistic regression model for cardiovascular events, we estimated the area under the receiver operating characteristic curve (C statistic) for natural logarithm-transformed hs-cTnT levels. Natural logarithm-transformed hs-cTnT level was added to baseline models of clinical risk factors (age; sex; current smoking; history of myocardial infarction, heart failure, revascularization, or diabetes mellitus; systolic and diastolic blood pressure; total and high-density lipoprotein cholesterol levels; body mass index; and eGFR) and clinical risk factors plus natural logarithm-transformed NT-proBNP and C-reactive protein levels. We calculated C statistics, category-free net reclassification improvement, and integrated discrimination improvement for these models.¹⁵⁻¹⁷ We evaluated model calibration with Hosmer-Lemeshow goodness-of-fit tests with 10 groups. All analyses were performed using commercially available software (STATA, version 12; StataCorp).

RESULTS

Among 984 participants, 794 (80.7%) had detectable levels of hs-cTnT (>5 pg/mL). With the standard troponin T assay, only 58 participants (5.9% of the entire cohort) had detectable troponin levels.² Age, sex, hypertension, history of heart failure, diabetes mellitus, or revascularization, physical inactivity, blood pressure, eGFR, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and diuretics, and levels of NT-proBNP and C-reactive protein varied across levels of hs-cTnT (**Table 1**).

Elevated hs-cTnT level was associated with greater severity of cardiac structural and functional abnormalities as measured by left ventricular mass index, left ventricular ejection fraction, left atrial function index, diastolic dysfunction, inducible ischemia, and treadmill exercise capacity (**Table 2**).

During a median follow-up of 8.2 (interquartile range, 3.7-9.0) years, 133 participants experienced myocardial infarction, 180 had hospital visits for heart failure, 146 died of cardiovascular causes, and 317 experienced the primary outcome of cardiovascular events (myocardial infarction, heart failure, or cardiovascular death).

Participants with intermediate or high hs-cTnT levels were more likely to experience secondary cardiovas-

cular events than were those with low hs-cTnT levels (**Figure 1**). For the individual components of the primary outcome (myocardial infarction, heart failure, and cardiovascular death), we found that higher hs-cTnT levels were associated with higher rates of cardiovascular events (**Figure 2**). Participants in the intermediate tertile of hs-cTnT level experienced cardiovascular events at 1.75 times the rate of participants in the lowest tertile of hs-cTnT level (hazard ratio [HR], 1.75 [95% CI, 1.23-2.47]; $P = .002$). Participants in the highest tertile of hs-cTnT level experienced cardiovascular events at 5 times the rate of participants in the lowest tertile of hs-cTnT level (HR, 5.19 [95% CI, 3.80-7.09]; $P < .001$).

After adjustment for clinical risk factors (age; male sex; smoking; history of hypertension, heart failure, diabetes mellitus, or revascularization; physical inactivity; systolic and diastolic blood pressure; eGFR; and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, and diuretics) and stress echocardiographic variables (left ventricular mass index, left ventricular ejection fraction, left atrial function index, diastolic dysfunction, inducible ischemia, and treadmill exercise capacity), a high hs-cTnT level remained associated with a 76% higher rate of cardiovascular events (adjusted HR, 1.76 [95% CI, 1.07-2.88]; $P = .03$). When participants were categorized by sex-specific tertiles of hs-cTnT levels, this association was similar (adjusted HR for highest vs lowest tertiles, 2.04 [95% CI, 1.28-3.25]; $P = .003$) (eTable 1; <http://www.jamainternalmed.com>).

When we evaluated continuous values of hs-cTnT with Cox proportional hazards regression models, we found that each doubling in hs-cTnT level was associated with almost twice the rate of cardiovascular events (HR, 1.98 [95% CI, 1.80-2.17]; $P < .001$) (**Table 3**). With adjustment for clinical risk factors (age; male sex; smoking; history of hypertension, heart failure, diabetes mellitus, or revascularization; physical inactivity; systolic and diastolic blood pressure; eGFR; and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, and diuretics), echocardiogram measurements (left ventricular mass index, left ventricular ejection fraction, left atrial function index, diastolic dysfunction, inducible ischemia, and treadmill exercise capacity), and cardiovascular biomarkers (NT-proBNP and C-reactive protein levels), each doubling in hs-cTnT level remained independently associated with a 37% greater risk of cardiovascular events (HR, 1.37 [95% CI, 1.14-1.65]; $P = .001$).

In unadjusted analysis, the association between hs-cTnT level and cardiovascular events was modified by sex ($P = .008$ for interaction). For each doubling in hs-cTnT level, women had greater increases in rates of cardiovascular events (HR, 2.64 [95% CI, 2.09-3.34]; $P < .001$) than did men (1.89 [1.70-2.10]; $P < .001$). However, after adjustment for echocardiogram measures, sex no longer significantly modified the association between hs-cTnT level and cardiovascular events ($P = .54$ for interaction) (eTable 2). We found no evidence of an interaction of hs-cTnT level with age, smoking, history of diabetes mellitus, eGFR, left ventricular

Table 1. Baseline Characteristics of 984 Participants by Tertile of hs-cTnT Level^a

Characteristic	Tertile of hs-cTnT Level			P Value
	Low (<5.00-7.09 pg/mL)	Intermediate (7.12-13.67 pg/mL)	High (13.78-540.20 pg/mL)	
No. of patients	330	326	328	
Demographics				
Age, mean (SD), y	60.6 (9.8)	68.1 (9.9)	71.5 (10.3)	<.001
Male sex	225 (68.2)	277 (85.0)	300 (90.5)	<.001
White	188 (57.0)	200 (61.3)	205 (62.5)	.34
Current smoking	99 (30.0)	55 (16.9)	42 (12.8)	<.001
History				
Hypertension	217 (65.8)	231 (70.9)	245 (74.7)	.05
Myocardial infarction	163 (49.4)	174 (53.4)	189 (57.6)	.14
Heart failure	36 (10.9)	48 (14.7)	89 (27.1)	<.001
Diabetes mellitus	55 (16.7)	79 (24.2)	124 (37.8)	<.001
Revascularization	168 (50.9)	205 (62.9)	202 (61.6)	.004
Depressive symptoms	67 (20.3)	59 (18.1)	64 (19.5)	.77
Physical inactivity	117 (35.5)	101 (31.0)	142 (43.3)	.004
Measurements, mean (SD)				
Body mass index ^b	28.5 (5.7)	28.5 (5.2)	28.3 (5.2)	.90
Blood pressure, mm Hg				
Systolic	130.6 (19.0)	133.3 (21.1)	135.1 (22.7)	.02
Diastolic	75.9 (10.4)	73.9 (11.1)	74.0 (12.4)	.04
eGFR, mL/min	84.1 (17.6)	71.8 (17.0)	55.8 (21.7)	<.001
Cholesterol level, mg/dL				
Total	181.5 (41.4)	176.0 (40.9)	175.5 (45.9)	.15
HDL	46.7 (14.2)	45.9 (13.6)	44.4 (14.3)	.11
Medication use				
β-Blocker	181 (54.8)	189 (58.0)	194 (59.1)	.68
ACEI or ARB	129 (39.1)	175 (53.7)	200 (61.0)	<.001
Statin	200 (60.6)	225 (69.0)	205 (62.5)	.09
Aspirin	233 (70.6)	244 (74.8)	231 (70.4)	.39
Diuretic	62 (18.8)	84 (25.8)	145 (44.2)	<.001
Biomarker				
NT-proBNP level, median (IQR), pg/mL	86 (45-182)	174 (87-358)	473 (175-1246)	<.001
C-reactive protein level, median (IQR), mg/L	2.0 (0.8-4.3)	2.0 (0.8-4.4)	2.7 (1.2-6.3)	.02

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; NT-proBNP, N-terminal portion of the prohormone of brain-type natriuretic peptide.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; C-reactive protein to nanomoles per liter, multiply by 9.524; cTnT to micrograms per liter, multiply by 0.001; and NT-proBNP to nanograms per liter, multiply by 1.

^aUnless otherwise indicated, data are expressed as number (percentage) of patients. Tertile ranges reflect actual values observed in the study population.

^bCalculated as weight in kilograms divided by height in meters squared.

Table 2. Structural and Functional Measures of Cardiac Disease Severity by Tertile of hs-cTnT Levels

Cardiac Measure	No. of Patients	Tertile of hs-cTnT Level ^a		
		Low (<5.00-7.09 pg/mL)	Intermediate (7.12-13.67 pg/mL)	High (13.78-540.20 pg/mL)
Left ventricular mass index ^b	975	89.5 (20.9)	94.8 (22.2)	110.4 (30.5)
Left ventricular ejection fraction, %	958	64.1 (7.1)	62.5 (9.2)	58.2 (11.4)
Left atrial function index ^c	944	45.5 (17.3)	40.6 (17.3)	34.2 (19.7)
Diastolic dysfunction, No. (%)	872	21/294 (7.1)	28/294 (9.5)	59/284 (20.8)
Inducible ischemia, No. (%)	898	47/307 (15.3)	74/307 (24.1)	97/284 (34.2)
Treadmill exercise capacity, metabolic equivalents	904	8.6 (3.6)	7.4 (3.0)	5.9 (2.9)

Abbreviation: hs-cTnT, high-sensitivity cardiac troponin T.

SI conversion factor: To convert cTnT to cTnT to micrograms per liter, multiply by 0.001.

^aUnless otherwise indicated, data are expressed as mean (SD). Tertile ranges reflect actual values observed in the study population. For all differences between tertiles, *P* < .001.

^bDefined as left ventricular mass in grams indexed to body surface area in meters squared.

^cDefined as [(left atrial emptying fraction × left ventricular outflow tract-velocity time integral)]/left atrial end-systolic volume index, where the left atrial emptying fraction was defined as the difference between the left atrial end-systolic volume and the left atrial end-diastolic volume divided by the left atrial end-systolic volume, presented in units.

ejection fraction, or left ventricular mass as predictors of cardiovascular events (*P* > .05 for all).

We evaluated discrimination and reclassification with the addition of hs-cTnT level. With hs-cTnT level alone,

the C statistic was 0.73 (95% CI, 0.69-0.76). Compared with a baseline model of clinical risk factors (age; sex; current smoking; history of myocardial infarction, heart failure, revascularization, or diabetes mellitus; systolic and diastolic blood pressure; levels of total and high-density lipoprotein cholesterol; body mass index; and eGFR), the addition of hs-cTnT level increased the C statistic from 0.72 (95% CI, 0.66-0.74) to 0.75 (0.70-0.77) ($P = .002$), resulting in a category-free net reclassification improvement of 33% (19%-49%) and an integrated discrimination improvement of 3.8% (1.7%-6.7%) (**Table 4**). Compared with a baseline model of clinical risk factors plus NT-proBNP and C-reactive protein levels, the addition of hs-cTnT level increased the C statistic from 0.76 (95% CI, 0.72-0.79) to 0.78 (0.74-0.80) ($P = .08$), resulting in a category-free net reclassification improvement of 13% (0.2%-32%) and an integrated discrimination improvement of 1.3% (0.2%-3.1%). We found no evidence of poor calibration in any model (all goodness-of-fit tests, $P > .10$).

COMMENT

In a sample of 984 outpatients with stable CHD, we found that elevated levels of hs-cTnT were associated with structural and functional measures of heart disease, including increased left ventricular mass index, lower left ventricular ejection fraction, reduced left atrial function index, diastolic dysfunction, inducible ischemia, and poor treadmill exercise capacity. After adjustment for these and other measures, hs-cTnT levels remained independently predictive of secondary cardiovascular events. These findings suggest that hs-cTnT levels quantify an element of risk that is not captured by existing measures of cardiovascular disease severity.

Two previous studies^{5,18} have evaluated the association between hs-cTnT level and secondary cardiovascular events in patients with stable CHD. In a relatively low-risk clinical trial population of patients with stable CHD, Omland et al⁵ found that levels of troponin detected with an hs-cTnT assay were associated with subsequent cardiovascular events and improved risk prediction. A study by Koenig et al¹⁸ of patients on discharge from cardiac rehabilitation confirmed these findings. Another study¹⁹ found that elevated levels of a different assay (high-sensitivity troponin I) were associated with secondary events in a clinical trial population of patients with stable CHD. Our study confirms and extends these findings in 3 important ways. First, we have found that hs-cTnT is detectable in more than three-fourths of patients in a general population of outpatients with CHD. Second, we have shown that hs-cTnT level is associated with cardiac structural and functional abnormalities. Third, we have demonstrated that, even after adjustment for available measures of cardiac disease severity, hs-cTnT level is associated with secondary cardiovascular events in a contemporary cohort of patients with stable CHD. Measurement of hs-cTnT levels may capture more elusive disease, such as microvascular ischemia, inflammation, or wall stress. In a study of patients with stable CHD undergoing cardiac computed tomography, hs-cTnT levels were not associated with stenosis severity but were associated with

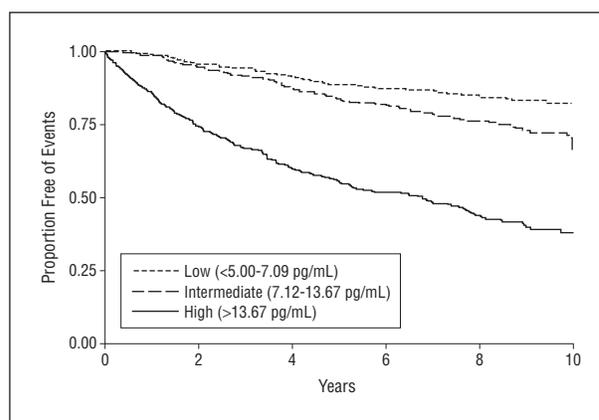


Figure 1. Combined cardiovascular events outcomes (myocardial infarction, heart failure, or cardiovascular death) by tertile of high-sensitivity cardiac troponin T (hs-cTnT) level (actual ranges observed in the study population). $P < .001$ by log-rank test. To convert hs-cTnT levels to micrograms per liter, multiply by 0.001.

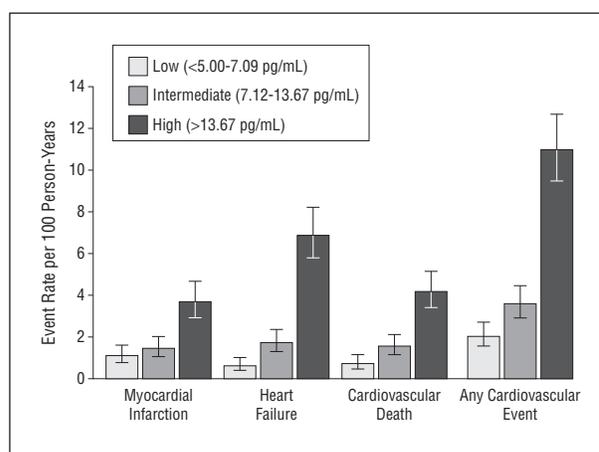


Figure 2. Rates of separate and combined cardiovascular events outcomes (myocardial infarction, heart failure, or cardiovascular death) by tertile of high-sensitivity cardiac troponin T (hs-cTnT) level (actual ranges observed in the study population). Error bars indicate 95% confidence intervals for event rates. $P < .001$ by test for trend for all events. To convert hs-cTnT levels to micrograms per liter, multiply by 0.001.

noncalcified plaque, implicating clinically silent plaque rupture and microembolism as a potential mechanism for myocardial injury and hs-cTnT release.²⁰

In addition, our findings align with studies of hs-cTnT in higher- and lower-risk populations. The finding that hs-cTnT level was associated with heart failure and death complements previous research in higher-risk outpatients with chronic heart failure, most of whom had ischemic heart disease.²¹ The finding that levels of hs-cTnT below the 99th percentile for a healthy population were associated with cardiovascular events also is consistent with data from prospective cohort studies of lower-risk, mostly healthy individuals.^{4,22,23}

Because participants in this study underwent exercise treadmill testing with stress echocardiography, we were able to evaluate the associations between measures of cardiac structure and function and levels of hs-cTnT. Previous studies have shown that left ventricular mass, left ventricular ejection fraction, and left atrial size were associated with hs-cTnT levels in the

Table 3. Association of hs-cTnT Level (per Doubling) With Cardiovascular Events After Adjusting for Clinical Risk Factors and Measures of Disease Severity

	Myocardial Infarction		Heart Failure		Cardiovascular Death		Any Event	
	HR (95% CI) ^a	P Value						
Unadjusted	1.74 (1.50-2.03)	<.001	2.30 (2.04-2.59)	<.001	1.95 (1.70-2.23)	<.001	1.98 (1.80-2.17)	<.001
Model No.								
1 ^b	1.55 (1.26-1.91)	<.001	1.92 (1.62-2.28)	<.001	1.78 (1.46-2.16)	<.001	1.68 (1.47-1.92)	<.001
2 ^c	1.32 (1.02-1.71)	.03	1.55 (1.19-2.01)	.001	1.39 (1.06-1.83)	.02	1.42 (1.19-1.70)	<.001
3 ^d	1.28 (0.99-1.67)	.06	1.44 (1.10-1.89)	.007	1.36 (1.03-1.81)	.03	1.37 (1.14-1.65)	.001

Abbreviations: hs-cTnT, high-sensitivity cardiac troponin T; HR, hazard ratio.

^aHazard ratio for cardiovascular events per doubling in hs-cTnT.

^bAdjusted for age; male sex; smoking; history of hypertension, heart failure, diabetes mellitus, or revascularization; physical inactivity; systolic and diastolic blood pressure; estimated glomerular filtration rate; and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, and diuretics.

^cAdjusted for model 1 variables plus left ventricular mass index, left ventricular ejection fraction, left atrial function index, diastolic dysfunction, inducible ischemia, and treadmill exercise capacity.

^dAdjusted for model 2 variables plus the natural logarithm of the N-terminal portion of the prohormone of brain-type natriuretic peptide and C-reactive protein levels.

Table 4. Discrimination and Risk Reclassification for Cardiovascular Events With the Addition of Biomarkers to a Clinical Risk Factor Model

	C Statistic (95% CI)	Improvement (95% CI), %	
		Integrated Discrimination	Category-free Net Reclassification
Clinical risk factors ^a	0.72 (0.66 to 0.74)	Reference	Reference
Added variables			
NT-proBNP level	0.76 (0.71 to 0.78) ^b	6.4 (3.4 to 10.3)	48 (30 to 63)
CRP level	0.72 (0.66 to 0.75) ^c	0.4 (-0.1 to 1.7)	12 (-6 to 28)
hs-cTnT level	0.75 (0.70 to 0.77) ^d	3.8 (1.7 to 6.7)	33 (19 to 49)
NT-proBNP + CRP levels	0.76 (0.72 to 0.79) ^e	6.4 (3.4 to 9.8)	49 (28 to 59)
NT-proBNP + CRP + hs-cTnT levels	0.78 (0.74 to 0.80) ^f	1.3 (0.2 to 3.1) ^g	13 (0.2 to 32) ^g

Abbreviations: CRP, C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal portion of the prohormone of brain-type natriuretic peptide.

^aInclude age; sex; current smoking; history of myocardial infarction, heart failure, diabetes mellitus, or revascularization; systolic and diastolic blood pressure; levels of total and high-density lipoprotein cholesterol; body mass index; and estimated glomerular filtration rate.

^bP < .001 for comparison with the clinical risk factor model.

^cP = .57 for comparison with the clinical risk factor model.

^dP = .002 for comparison with the clinical risk factor model.

^eP < .001 for comparison with the clinical risk factor model.

^fP = .08 for comparison with the model including clinical risk factors, NT-proBNP + CRP.

^gIndicates improvement in reference to the model including clinical risk factors, NT-proBNP + CRP.

general population.^{4,22} In addition to finding that cardiac structure was associated with hs-cTnT levels, we revealed that functional measures of cardiac disease, including left ventricular ejection fraction, left atrial function index, diastolic dysfunction, inducible ischemia, and treadmill exercise capacity, were associated with hs-cTnT levels. This finding suggests that hs-cTnT levels are related to structural and functional cardiac abnormalities.

We found that the association between hs-cTnT levels and cardiovascular events was modified by sex in the unadjusted analysis. Levels of hs-cTnT are known to vary between women and men, and this variation is suspected to be related to heart size.²⁴ An analysis of hs-cTnT levels in a prospective cohort study of participants without cardiovascular disease at baseline also noted an interaction between sex and hs-cTnT levels.²³ In our study, higher hs-cTnT levels were associated with a higher rate of cardiovascular events in women than in men, but the interaction between sex and hs-cTnT levels was no

longer statistically significant after adjustment for measures of cardiac structure and function.

Our study has several limitations. First, our population included mostly urban men; thus, the results may not be generalizable to other populations. The finding that sex differences in hs-cTnT levels modified the association with cardiovascular events but may be related to cardiac structure and function should be validated in populations including more women. Second, we analyzed data from the full range of hs-cTnT levels, including those levels ranging from 5 to 14 pg/mL, where the coefficient of variation for the assay is greater than 10%. This method limits the precision of our results within this range of values. However, the finding that participants with intermediate levels of hs-cTnT had higher event rates than participants in the lowest tertile of hs-cTnT levels suggests that measurement of hs-cTnT in this range can provide prognostic information. Finally, we did not report values higher than the assay limit of blank but below the limit of detection (3-5 pg/mL), which differs from previous reports of hs-

cTnT levels but is more reflective of the range of values in which hs-cTnT can be detected.

In conclusion, we found that levels of hs-cTnT were associated with measures of cardiac structure and function and with cardiovascular events independent of clinical risk factors, echocardiographic measures of heart disease, exercise capacity, and biomarkers. These findings support the potential use of hs-cTnT as a marker of risk in stable outpatients with CHD.

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