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Prognostic Value of Cardiac Troponin I Measured With a Highly Sensitive Assay in Patients With Stable Coronary Artery Disease

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Objectives The aims of this study were to assess the prognostic value of cardiac troponin I levels, measured with a new high-sensitivity assay, in low-risk patients with stable coronary artery disease (CAD) and to contrast its determinants and prognostic merit with that of high-sensitivity cardiac troponin T (hs-TnT).

Background New, highly sensitive cardiac troponin assays permit evaluation of the association between troponin levels and outcomes in patients with stable CAD.

Methods High-sensitivity cardiac troponin I (hs-TnI) levels at baseline were assessed in 3,623 patients with stable CAD and preserved systolic function enrolled in the PEACE (Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy) trial.

Results In total, 98.5% of patients had hs-TnI concentrations higher than the detection level (1.2 pg/ml). hs-TnI correlated moderately with hs-TnT ($r = 0.44$) and N-terminal pro–B-type natriuretic peptide ($r = 0.39$) but only weakly with age ($r = 0.17$) and estimated glomerular filtration rate ($r = -0.11$). During a median follow-up period of 5.2 years, 203 patients died of cardiovascular causes or were hospitalized for heart failure, and 209 patients had nonfatal myocardial infarctions. In analyses adjusting for conventional risk markers, N-terminal pro–B-type natriuretic peptide, and hs-TnT, hs-TnI levels in the fourth compared with the 3 lower quartiles were associated with the incidence of cardiovascular death or heart failure (hazard ratio: 1.88; 95% confidence interval: 1.33 to 2.66; $p < 0.001$). There was a significant, albeit weaker association with nonfatal myocardial infarction (hazard ratio: 1.44; 95% confidence interval: 1.03 to 2.01; $p = 0.031$). In the same models, hs-TnT concentrations were associated with the incidence of cardiovascular death or heart failure but not of myocardial infarction.

Conclusions In patients with stable CAD, hs-TnI concentrations are associated with cardiovascular risk independently of conventional risk markers and hs-TnT. (Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy [PEACE]; NCT00000558) (J Am Coll Cardiol 2013;xx:xxx) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

AMI = acute myocardial infarction

CAD = coronary artery disease

CI = confidence interval

CRP = C-reactive protein

cTnI = cardiac troponin I

cTnT = cardiac troponin T

GFR = glomerular filtration rate

HR = hazard ratio

hs-TnI = high-sensitivity cardiac troponin I

hs-TnT = high-sensitivity cardiac troponin T

LV = left ventricular

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

PEACE = Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy

In patients with acute chest pain, measurement of cardiac troponin I (cTnI) or cardiac troponin T (cTnT) is routinely used to diagnose acute myocardial infarction (AMI) (1). In the setting of acute coronary syndromes, troponin elevation also provides information concerning the risk for subsequent adverse cardiovascular events, as well as the benefit of therapeutic intervention (2). The introduction of high-sensitivity assays permits the accurate determination of very low levels of circulating cardiac troponins (3). Using a highly sensitive assay for cTnT, we recently demonstrated the presence of detectable levels in a large proportion of patients with stable coronary artery disease (CAD) (4). Moreover, cTnT concentrations were independently associated with the incidence of cardiovascular death and heart failure in these patients.

Although conventional cTnT and cTnI assays have been commonly considered to provide comparable diagnostic information in acute coronary syndromes (5), recent studies comparing the diagnostic value of highly sensitive assays for cTnT and cTnI have revealed interesting differences with potential clinical implications (6). Moreover, acute ischemia may have differential effects on cTnT (7) and cTnI (8) release. Recent data from asymptomatic subjects at high risk for atherosclerotic events suggest that cTnI provides independent information concerning the risk for future AMI (9), whereas in another study, the association between cTnT and the risk for AMI in patients with stable CAD was weak and not significant after adjustment for confounders (4). Taken together, these observations suggest that factors influencing low-level, chronic troponin elevation may differ between cTnT and cTnI. Whether the potential differences in chronic release and degradation patterns have prognostic consequences is unknown. Moreover, whether cTnI provides complementary prognostic information to cTnT in patients with stable CAD has not been evaluated.

Accordingly, the objectives of the present study of a large cohort of patients with stable CAD and preserved left ventricular (LV) ejection fractions were first to assess the determinants and prognostic value of circulating cTnI measured using a prototype high-sensitivity assay and second to contrast the results with those obtained using a high-sensitivity assay for cTnT.

Methods

Study design and patients. This is a biomarker substudy of the PEACE (Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy) trial. The design, entry criteria, and main results of this trial have been described previously (10). In summary, from November 1996 to June 2000, 8,290 patients were randomized to receive either the angiotensin-converting enzyme inhibitor trandolapril or placebo. Entry criteria were age ≥50 years, documented CAD, and LV ejection fraction >40%; qualitatively normal results on left ventriculography; or the absence of LV wall motion abnormalities on echocardiography. None of the patients had been hospitalized with unstable angina during the preceding 3 months. All patients included were deemed to be free of heart failure at the time of randomization. All patients who had baseline ethylenediamine-tetraacetic acid plasma samples available for measurement of high-sensitivity cTnT (hs-cTnT) and serum samples available for determination of high-sensitivity cTnI (hs-TnI) (n = 3,623) were included in the present substudy. The institutional review boards of the participating sites reviewed and approved the study, and all participants provided written informed consent.

On the basis of prior data concerning the prognostic value of hs-TnT in patients with stable CAD, the primary outcomes examined in the present analysis were 1) a composite of cardiovascular death and nonfatal heart failure and 2) nonfatal AMI (4). Cardiovascular death and nonfatal AMI were pre-specified endpoints of the PEACE trial. To ascertain these endpoints, medical records were reviewed by a central, blinded morbidity and mortality committee. Heart failure was classified by local staff members and confirmed by the coordinating center through review of medical records and required hospitalization with heart failure as the primary diagnosis. Clinical events were all classified before biomarker measurement.

Blood sampling procedures and biochemical assays. Samples of venous blood were obtained before randomization. The test tube was centrifuged at room temperature, and serum and plasma were aspirated and frozen at −20°C at individual centers. Within 3 months of collection, serum and plasma samples were shipped on dry ice to the central laboratory for storage at −70°C or colder, pending analysis. For hs-TnI and hs-TnT analysis, samples were shipped on dry ice to Akershus University Hospital (Lørenskog, Norway).

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hs-TnI in serum was determined using a prototype cTnI assay from Abbott Diagnostics (Lake Forest, IL): ARCHITECT STAT High Sensitive Troponin. The level of detection for this assay has been reported to be 1.2 pg/ml (range: 0 to 50,000 pg/ml), with a coefficient of variation of 10% observed at a concentration of 3.0 pg/ml, and the diagnostic cutoff representing the 99th percentile in the general population is 15.6 pg/ml in women and 34.2 pg/ml in men (3). Levels lower than the detection limit were assigned a value of 1.2 pg/ml.

hs-TnT, N-terminal pro–B-type natriuretic peptide (NT-proBNP), and C-reactive protein (CRP) concentrations in plasma were determined as described previously (4,11). Glomerular filtration rate (GFR) was estimated using the 4-variable Modification of Diet in Renal Disease equation (12). All biochemical testing was performed by experienced laboratory personnel blinded to clinical outcomes and treatment allocation.

Statistical analysis. Sex-specific quartiles of hs-TnI were calculated. Highly skewed variables (hs-TnI, hs-TnT, CRP, and NT-proBNP) were successfully logarithmically transformed to normalize the distribution. Comparisons of baseline characteristics across the different sex-specific quartiles of hs-TnI were done using the test for trend for continuous variables and the Cochran-Armitage test for categorical variables. For continuous variables, each case was assigned a rank, and the median value within each quartile and the correlation between this value and the category number were calculated. Pearson's correlations were used to test the relationships between continuous variables. Determinants of hs-TnI and hs-TnT levels were further examined by generating multivariate linear regression models. Variables identified in univariate analyses with $p < 0.20$ were entered into the multivariate model, which was further reduced by the F-ratio test. Cox proportional hazards regression models were estimated to test the relationships between hs-TnI and the composite outcome of cardiovascular death or nonfatal heart failure and between hs-TnI and nonfatal AMI. Patients were censored at their last visits. Cox models for hs-TnI were initially adjusted for treatment assignment and baseline variables known to be important predictors of cardiovascular events: age, sex, body mass index, ejection fraction <50%, estimated GFR, current smoking, history of hypertension, history of diabetes, history of AMI, history of percutaneous coronary intervention, history of coronary artery bypass grafting, history of stroke, history of transient ischemic attack, history of intermittent claudication, serum total cholesterol, high-sensitivity CRP, use of a beta-blocker, use of a lipid-lowering drug, use of aspirin or an antiplatelet medication, and use of a diuretic medication. Models were reduced using the stepwise selection method with the Akaike information criterion applied at each step (13). Estimates of the C-index for the Cox regression models were calculated according to the method of Pencina and D'Agostino (14). The discriminative value was examined using the integrated discrimination improvement measure, estimating the change in the predicted survival probabilities after the inclusion of hs-TnI or hs-TnT to the models in patients with and without events (15). Cumulative incidence plots categorized according to the sex-specific quartiles of hs-TnI were generated. A p value <0.05 was considered to be statistically significant, and all tests were 2 sided. SAS version 9.2 (SAS Institute Inc., Cary, North Carolina), SPSS version 16.0 (SPSS, Inc., Chicago, Illinois) and Stata version 11.0 (StataCorp LP, College Station, Texas) were used for analyses.

Results

Distribution and determinants of hs-TnI. Concentrations of hs-TnI at or above the limit of detection of the assay (1.2 pg/ml) were observed in 3,567 patients (98.5%), whereas concentrations of hs-TnI at or above the sex-specific 99th percentile of a general population (15.6 pg/ml in women and 34.2 pg/ml in men) were evident in 105 patients (2.9%). In comparison, concentrations of hs-TnT at or above the sex-specific 99th percentile of a general population (14.2 pg/ml in men and 10.0 pg/ml in women) were evident in 395 of 3,679 patients (10.9%). The distribution patterns of hs-TnI and hs-TnT are depicted in Figure 1.

Characteristics of the patients according to the sex-specific quartiles of hs-TnI concentrations at baseline are shown in Table 1. Increasing quartiles of hs-TnI were associated with a number of conventional risk markers. By Pearson's correlation, logarithmically transformed hs-TnI levels were correlated moderately with hs-TnT ($r = 0.44$) and NT-proBNP ($r = 0.39$) but only weakly with age ($r = 0.17$) and estimated GFR ($r = -0.11$). In contrast, the associations of hs-TnT with age ($r = 0.33$) and estimated GFR ($r = -0.16$) were somewhat more robust.

To assess the relative contribution of potential determinants of troponin levels, separate series of linear regression analyses were conducted with logarithmically transformed hs-TnI and hs-TnT concentrations as the dependent variables, respectively. By univariate linear regression analyses, a number of conventional risk markers and risk factors were associated with higher logarithmically transformed concentrations of both hs-TnI and hs-TnT (Table 2). However, the strength of associations differed somewhat between hs-TnI and hs-TnT for several variables. For instance, a history of AMI was significantly associated with hs-TnI ($p < 0.0001$) but not hs-TnT ($p = 0.79$), whereas current smoking was inversely related to hs-TnT ($p < 0.0001$) but not to hs-TnI ($p = 0.07$). Moreover, by multivariate linear regression analysis, history of AMI was identified as independently associated with hs-TnI but not hs-TnT. Conversely, the association with eGFR was significant for hs-TnT ($p < 0.0001$) but not for hs-TnI ($p = 0.06$). The associations with age and sex also appeared to be somewhat stronger for hs-TnT than for hs-TnI (Table 2).

hs-TnI and the incidence of cardiovascular death or nonfatal heart failure. During a median follow-up period of 5.2 years, there were 203 (5.6%) cardiovascular deaths or

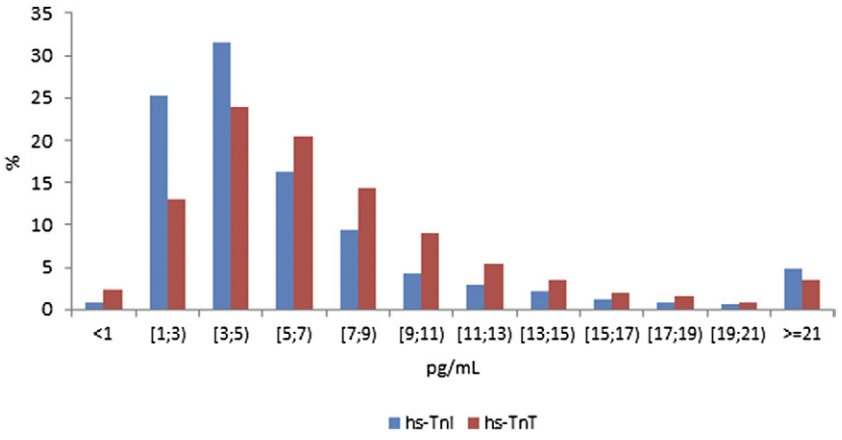

Figure 1 **Distribution Patterns of hs-TnI and hs-TnT in Stable CAD**

The patterns of distribution of high-sensitivity cardiac troponin I (hs-TnI) and high-sensitivity cardiac troponin T (hs-TnT) in 3,263 patients with stable coronary artery disease (CAD) differed slightly. Concentrations of hs-TnI at or above the limit of detection of the assay (1.2 pg/ml) were observed in 3,567 patients (98.5%). A lower proportion of patients had concentrations of hs-TnI at or above the sex-specific 99th percentile of a general population (2.9%) than was observed for hs-TnT (10.9%). The sex-specific 99th-percentile values of a general population are 15.6 pg/ml in women and 34.2 pg/ml in men for hs-TnI and 10.0 pg/ml in women and 14.2 pg/mL in men for hs-TnT.

first hospitalizations for heart failure. The association between hs-TnI levels by quartiles and the cumulative incidence of cardiovascular death or heart failure is displayed in Figure 2. By univariate analysis, there was a strong and graded association between hs-TnI levels at baseline and the incidence of cardiovascular death or heart failure (hazard ratio [HR] per 1-SD increase in the natural logarithm of hs-TnI: 1.68; 95% confidence interval [CI]: 1.54 to 1.84]; $p < 0.0001$). In the final multivariate model that adjusted for age, sex, ejection fraction <50%, estimated GFR, current smoking, serum cholesterol, prior hypertension, diabetes, AMI, percutaneous coronary intervention, arterial claudication, aspirin use, and serum cholesterol, as well as for CRP and NT-proBNP, the association remained strong and highly significant (HR: 1.34; 95% CI: 1.19 to 1.51; $p < 0.0001$).

When considering cardiovascular death and nonfatal heart failure as separate endpoints, similar relationships were observed. Thus, the crude and adjusted HRs for the association between hs-TnI as a log-transformed continuous variable and cardiovascular death were 1.79 (95% CI: 1.54 to 2.08; $p < 0.0001$) and 1.38 (95% CI: 1.13 to 1.68; $p = 0.002$), respectively. Corresponding HRs for the endpoint of nonfatal heart failure were 2.16 (95% CI: 1.85 to 2.52; $p < 0.0001$) and 1.55 (95% CI: 1.25 to 1.91; $p < 0.0001$).

The association between increasing quartiles of hs-TnI and hs-TnT and the incidence of cardiovascular death or heart failure suggested threshold effects corresponding to the 75th percentile (Fig. 2). Dichotomizing patients according to this hs-TnI level, the crude HR for patients in the fourth quartile compared with the 3 lower quartiles was 4.18 (95% CI: 3.15 to 5.54; $p < 0.0001$). The association remained highly significant after multivariate adjustment (HR: 2.12; 95% CI: 1.54 to 2.93; $p < 0.0001$). Similar results were obtained when considering cardiovascular death and nonfatal heart failure as individual endpoints. Thus, the adjusted HRs were 2.01 (95% CI: 1.33 to 3.05; $p = 0.001$) for cardiovascular death and 2.14 (95% CI: 1.32 to 3.49; $p = 0.002$) for nonfatal heart failure.

hs-TnI and the incidence of nonfatal myocardial infarction. During follow-up, there were 209 hospitalizations for nonfatal AMI. By univariate analysis, the association between logarithmically transformed hs-TnI levels and AMI was less strong than the association with cardiovascular death or heart failure but still highly significant (HR: 1.30; 95% CI: 1.15 to 1.47; $p < 0.0001$). In the final multivariate model that adjusted for age, ejection fraction <50%, current smoking, prior hypertension, diabetes, and coronary artery bypass grafting, as well as for CRP and NT-proBNP, the association remained significant (HR: 1.20; 95% CI: 1.04 to 1.37; $p = 0.010$). Further adjustment for history of AMI did not alter the results. Dichotomizing patients according to the 75th percentile resulted in an unadjusted HR of 1.75 (95% CI: 1.31 to 2.35); after multivariate adjustment, the HR was 1.41 (95% CI: 1.03 to 1.94; $p = 0.014$).

Differential prognostic value of hs-TnI and hs-TnT. Forcing both hs-TnI and hs-TnT into the full multivariate models demonstrated that both variables, entered as continuous or as dichotomous variables (at the 75th-percentile cut points), provided strong and independent prognostic information for the combined endpoint of cardiovascular death and nonfatal congestive heart failure (Table 3). For the endpoint of nonfatal AMI, the association was highly significant for hs-TnI but not for hs-TnT (Table 4).

Table 1 Patient Characteristics by Quartile of hs-TnI

Variable	Quartile 1		Quartile 2		Quartile 3		Quartile 4		p Value for Trend
	Total No. of Patients	Value	Total No. of Patients	Value	Total No. of Patients	Value	Total No. of Patients	Value	
hs-TnI (pg/ml)									
Men	743	1.2–3.0	748	3.1–4.5	710	4.6–7.3	732	7.4–610.1	
Women	180	1.2–2.5	166	2.6–3.9	176	4.0–6.3	168	6.4–577.17	
Demographic characteristics									
Age (yrs)	923	61.7 ± 7.4	914	63.9 ± 7.9	886	65.0 ± 8.3	900	66.0 ± 8.4	<0.001
Women	923	180 (19.5%)	914	166 (18.2%)	886	176 (19.9%)	900	168 (18.7%)	
Body mass index (kg/m^2)	917	28.1 ± 4.5	910	28.3 ± 4.4	878	28.7 ± 5.0	899	29.0 ± 4.9	<0.001
Medical history									
Documented myocardial infarction	923	425 (46.0%)	914	509 (55.7%)	885	560 (63.3%)	900	554 (61.6%)	<0.001
Angina pectoris	923	694 (75.2%)	914	663 (72.5%)	885	639 (72.2%)	900	645 (71.7%)	0.255
Percutaneous coronary intervention	922	464 (50.3%)	914	429 (46.9%)	885	420 (47.5%)	900	343 (38.1%)	0.072
Coronary artery bypass grafting	923	256 (27.7%)	914	286 (31.3%)	885	341 (38.5%)	900	394 (43.8%)	<0.001
Diabetes mellitus	923	135 (14.6%)	914	127 (13.9%)	885	142 (16.0%)	900	179 (19.9%)	0.037
Previous hypertension	923	325 (35.2%)	914	373 (40.8%)	885	425 (48.0%)	900	479 (53.2%)	<0.001
Intermittent claudication	923	63 (6.8%)	914	70 (7.7%)	885	91 (10.3%)	900	95 (10.6%)	0.049
TIA	923	25 (2.7%)	914	32 (3.5%)	885	24 (2.7%)	900	36 (4.0%)	0.224
Stroke	923	25 (2.7%)	914	36 (3.9%)	885	44 (5.0%)	899	50 (5.6%)	0.049
Current smokers	923	143 (15.5%)	913	145 (15.9%)	884	130 (14.7%)	900	125 (13.9%)	0.345
Mean blood pressure (mm Hg)									
Systolic	921	129.7 ± 15.2	914	131.5 ± 16.3	885	135.3 ± 17.0	900	137.2 ± 17.5	<0.001
Diastolic	921	77.8 ± 9.7	914	77.6 ± 10.0	885	78.6 ± 9.8	900	78.6 ± 10.2	<0.001
Laboratory determinations									
LVEF < 50%	827	154 (17.4%)	891	195 (21.9%)	866	246 (28.4%)	883	277 (31.4%)	<0.001
eGFR (ml/min/1.73 m^2)	922	81.9 ± 19.8	914	78.1 ± 17.7	883	77.0 ± 19.3	897	75.1 ± 19.8	<0.001
Serum cholesterol (mg/dl)	897	190.4 ± 39.3	875	193.0 ± 38.3	844	190.6 ± 38.5	862	193.9 ± 38.9	<0.001
CRP (mg/l)*	917	1.5 (1.4–1.6)	907	1.7 (1.5–1.8)	878	1.8 (1.7–1.9)	892	2.1 (1.9–2.2)	<0.001
NT-proBNP (pg/ml)*	917	84.5 (80.1–89.1)	903	114.9 (108.5–121.7)	876	169.2 (159.2–179.9)	890	254.4 (237.9–272.1)	<0.001
hs-TnT (pg/ml)	904	4.9 ± 4.1	879	5.8 ± 4.7	857	7.8 ± 4.7	873	11.7 ± 8.7	<0.001
Medications									
Assignment to trandolapril	923	453 (49.1%)	914	468 (51.2%)	886	440 (49.7%)	900	449 (49.9%)	0.474
Calcium-channel blockers	923	304 (32.9%)	914	312 (34.1%)	885	290 (32.8%)	899	298 (33.1%)	0.489
Beta-blockers	923	567 (61.4%)	914	579 (63.3%)	885	544 (61.5%)	899	555 (61.7%)	0.485
Aspirin or other antiplatelet medications	923	855 (92.6%)	914	844 (92.3%)	885	810 (91.5%)	899	799 (88.9%)	0.129
Lipid-lowering drugs	923	712 (77.1%)	914	649 (71.0%)	885	635 (71.8%)	898	603 (67.1%)	0.050

Values are mean ± SD or number (percent) except as indicated. *Values are geometric means (95% confidence intervals).

CRP = C-reactive protein; hs-TnT = high-sensitivity cardiac troponin T; eGFR = estimated glomerular filtration rate; hs-TnI = high-sensitivity cardiac troponin I; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; TIA = transient ischemic attack.

Table 2 Predictors of Circulating hs-TnI and hs-TnT

Determinant	Univariate Analysis		Multivariate Analysis*	
	hs-TnI: Standardized Beta (p)	hs-TnT: Standardized Beta (p)	hs-TnI: Standardized Beta (p)	hs-TnT: Standardized Beta (p)
Treatment assignment at baseline	0.008 (0.637)	0.029 (0.088)		
Age	0.169 (<0.001)	0.325 (<0.001)	0.041 (0.018)	0.239 (<0.001)
Sex	0.095 (<0.001)	0.176 (<0.001)	0.164 (<0.001)	0.248 (<0.001)
BMI	0.075 (<0.001)	0.044 (0.009)	0.017 (<0.001)	0.096 (<0.001)
LVEF <50%	−0.115 (<0.001)	−0.079 (<0.001)	−0.025 (0.112)	
eGFR	−0.109 (<0.001)	−0.155 (<0.001)	−0.025 (0.122)	−0.053 (0.001)
Current smoking	−0.030 (0.067)	−0.120 (<0.001)		−0.044 (0.004)
Previous hypertension	0.119 (<0.001)	0.106 (<0.001)	0.084 (<0.001)	0.062 (<0.001)
Documented myocardial infarction	0.117 (<0.001)	0.005 (0.781)	0.087 (<0.001)	
Diabetes mellitus	0.051 (0.002)	0.121 (<0.001)	0.034 (0.027)	0.113 (<0.001)
Intermittent claudication	0.054 (0.001)	0.057 (0.001)		
TIA	0.014 (0.397)	0.025 (0.147)		
Stroke	0.056 (0.001)	0.066 (<0.001)		
PCI	−0.096 (<0.001)	−0.103 (<0.001)	−0.036 (0.025)	−0.043 (0.004)
CABG	0.130 (<0.001)	0.134 (<0.001)	0.033 (0.048)	
Total cholesterol	0.020 (0.240)	0.057 (0.001)		
Use of beta-blockers	0.0002 (0.988)	−0.027 (0.110)		
Use of lipid-lowering drugs	−0.077 (<0.001)	−0.058 (0.001)		
Use of aspirin and antiplatelet medications	−0.057 (0.001)	−0.074 (<0.001)		
ln CRP	0.089 (<0.001)	0.046 (0.006)	0.027 (0.088)	
ln NT-proBNP	0.387 (<0.001)	0.298 (<0.001)	0.374 (<0.001)	0.234 (<0.001)
ln hs-TnT	0.442 (<0.001)			
ln hs-TnI		0.442 (<0.001)		

*Final models for logarithmically transformed hs-TnI and hs-TnT. Variables identified in univariate analyses with p <0.20 were entered into the multivariate model, which was further reduced by the F-ratio test. Multivariate models thus differ for hs-TnI and hs-TnT. Determination coefficients (r^2 values) for models for hs-TnI and hs-TnT were 0.461 and 0.483, respectively.

BMI = body mass index; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention. Other abbreviations as in Table 1.

After dichotomizing patients according to the sex-specific 99th-percentile values of a healthy reference population for hs-TnI (34.2 pg/ml in men and 15.6 pg/ml in women), the association remained highly significant after multivariate adjustment (HR: 1.96; 95% CI: 1.40 to 2.74; $p < 0.0001$). Using the sex-specific 99th-percentile values of a healthy reference population for hs-TnT (14.2 pg/ml in men and 10.0 pg/ml in women), the association was attenuated and borderline significant (HR: 1.43; 95% CI: 1.00 to 2.05; $p = 0.051$) (Table 5).

To assess whether the combined use of hs-TnT and hs-TnI permitted the identification of patients at particularly high risk, we estimated the HR for cardiovascular death or heart failure and for AMI in patients who had hs-TnI and hs-TnT concentrations greater than or equal to the sex-specific 75th percentile of healthy subjects (hs-TnI: 3.5 pg/ml in men, 2.8 pg/ml in women; hs-TnT: 5.6 pg/ml in men, 3.9 pg/ml in women) using patients who had concentrations of both hs-TnI and hs-TnT lower than the sex-specific 75th percentile of healthy subjects as the reference (Table 6). In addition, we estimated the HR of subjects with discordant values (i.e., those with concentrations greater than or equal to the sex-specific 75th percentile of healthy subject with 1 assay only) (Table 6). High levels of both hs-TnI and hs-TnT were associated with substantially increased risk for cardiovascular death or heart failure (HR: 7.57; 95% CI: 4.30 to 13.35), whereas the risk associated with high levels of either hs-TnI or hs-TnT was more moderate (HR: 2.25; 95% CI: 1.18 to 4.28).

Discrimination. For the endpoint of cardiovascular death or nonfatal congestive heart failure, the C-index of the multivariate model that included conventional risk markers, CRP, and NT-proBNP was 0.763 (95% CI: 0.725 to 0.801). Adding hs-TnI to the model resulted in a small but significant increase in the C-index (Table 7). Similar results were obtained for hs-TnT. For the endpoint of AMI, the C-index of the multivariate model that included CRP and NT-proBNP was 0.647 (95% CI: 0.597 to 0.696). Adding hs-TnI to the model did not significantly increase the C-index, nor did the addition of hs-TnT.

The integrated discrimination improvement values for these endpoints were also calculated. Adding hs-TnI to the models resulted in highly significant improvements in the performance of the models for cardiovascular death or nonfatal congestive heart failure (Table 7). Similar results were obtained for hs-TnT. Adding hs-TnI or hs-TnT to the models for AMI did not significantly improve the performance of the models.

Interaction with trandolapril therapy. No significant interaction was observed between concentration of hs-TnI or hs-TnT and the effect of trandolapril on the endpoint of cardiovascular death or heart failure. Moreover, trandolapril

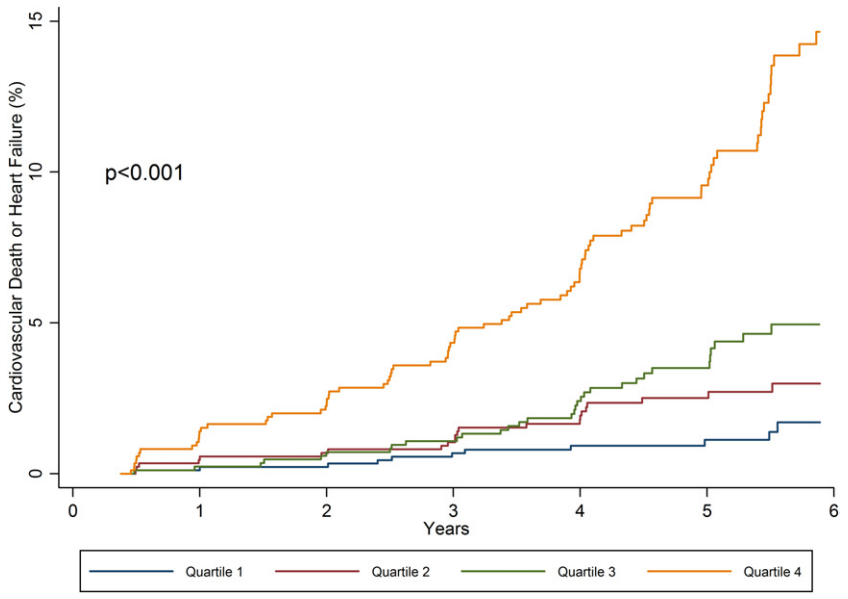

Figure 2 **Risk for Cardiovascular Death or Heart Failure by Baseline hs-TnI Level**

Cumulative incidence of the composite endpoint of cardiovascular death or hospitalization for heart failure by baseline concentrations of high-sensitivity cardiac troponin I (hs-TnI). There was a strong and graded association between increasing quartiles of cardiac troponin I and the risk for cardiovascular death or hospitalization for heart failure.

therapy was not associated with a significantly reduced incidence of the combined endpoint of cardiovascular death or heart failure in the small subgroup of patients who were in the fourth quartiles of both hs-TnI and hs-TnT (HR: 0.84; 95% CI: 0.59 to 1.21; p = 0.35).

Discussion

The main finding of the present study is that small elevations in hs-TnI are associated with the incidence of cardiovascular death or heart failure in patients with stable CAD and provide incremental prognostic information to conventional risk markers and prognostic cardiovascular biomarkers, including hs-TnT. Interestingly, the correlation between hs-TnI and hs-TnT concentrations was of only moderate strength, suggesting that mechanisms of release and/or degradation may potentially differ between the troponins in the chronic setting. Furthermore, hs-TnI, but not hs-TnT, was significantly and indepen-

Table 3 **Final Multivariate Cox Regression Models for Cardiovascular Death or Congestive Heart Failure**

	Fourth Quartile for hs-TnI and hs-TnT		Continuous hs-TnI and hs-TnT	
Variable	HR (95% CI)	p	HR (95% CI)	p
hs-TnI	1.88 (1.33–2.66)	<0.0001	1.18 (1.01–1.36)*	0.033
hs-TnT	1.43 (1.01–2.04)	0.045	1.51 (1.17–1.95)*	0.001
Age	1.04 (1.02–1.07)	<0.0001	1.04 (1.01–1.06)	0.001
LVEF < 50%	1.24 (0.90–1.70)	0.19	1.22 (0.89–1.68)	0.220
eGFR	1.00 (0.99–1.00)	0.37	1.00 (0.99–1.01)	0.423
Current smoking	1.64 (1.10–2.45)	0.016	1.60 (1.07–2.39)	0.022
History of hypertension	1.19 (0.87–1.63)	0.27	1.22 (0.90–1.67)	0.201
History of myocardial infarction	1.11 (0.81–1.52)	0.53	1.09 (0.79–1.51)	0.586
History of diabetes mellitus	1.74 (1.24–2.44)	0.001	1.71 (1.23–2.39)	0.002
History of CABG	1.54 (1.13–2.10)	0.007	1.45 (1.06–1.98)	0.019
Serum total cholesterol	1.00 (1.00–1.01)	0.085	1.00 (1.00–1.01)	0.041
History of intermittent claudication	1.73 (1.18–2.53)	0.005	1.61 (1.10–2.37)	0.015
Lipid-lowering therapy	0.70 (0.52–0.95)	0.024	0.70 (0.52–0.95)	0.024
ln NT-proBNP	1.52 (1.28–1.80)	<0.0001	1.55 (1.31–1.84)*	<0.0001
ln CRP	1.04 (0.90–1.24)	0.60	1.03 (0.89–1.21)*	0.671

*HRs based on a 1-SD change in the natural logarithm of troponin concentration.
CI = confidence interval; HR = hazard ratio. Other abbreviations as in Tables 1 and 2.

Table 4 Final Multivariate Cox Regression Models for Myocardial Infarction

Variable	Fourth Quartile for hs-TnI and hs-TnT		Continuous hs-TnI and hs-TnT	
	HR (95% CI)	p	HR (95% CI)	p
hs-TnI	1.44 (1.03–2.01)	0.031	1.21 (1.04–1.41)*	0.013
hs-TnT	0.93 (0.65–1.31)	0.67	0.97 (0.84–1.13)*	0.714
Age	1.01 (0.99–1.03)	0.25	1.01 (0.99–1.03)	0.262
LVEF < 50%	1.22 (0.89–1.66)	0.21	1.21 (0.89–1.65)	0.232
Current smoking	1.73 (1.22–2.46)	0.002	1.71 (1.21–2.43)	0.003
History of hypertension	1.19 (0.89–1.58)	0.24	1.19 (0.90–1.59)	0.227
History of diabetes mellitus	1.70 (1.21–2.37)	0.002	1.70 (1.22–2.38)	0.002
History of CABG	1.59 (1.17–2.17)	0.003	1.55 (1.14–2.12)	0.006
ln NT-proBNP	1.06 (0.90–1.25)	0.46	1.05 (0.89–1.23)	0.580
ln CRP	1.16 (1.01–1.34)	0.039	1.16 (1.00–1.34)	0.043

*HRs based on a 1-SD change in the natural logarithm of troponin concentration.
Abbreviations as in Tables 1 to 3.

dently associated with both prior AMI and the incidence of subsequent AMI.

Determinants of hs-TnI and hs-TnT in patients with stable CAD. Troponin I and T are components of the contractile apparatus of cardiomyocytes, but small quantities of free troponin I and T are also believed to be present in the cytoplasm as an early releasable pool (16). The troponin subunits each play a unique functional role, and it is also possible that different troponin fragments may have differential biological activity (16). Traditionally, cardiac troponins have been considered markers of myocardial necrosis, typically in the setting of acute coronary syndromes, but recent observations that very low levels of both cTnT and cTnI are found circulating in patients with stable CAD (4), and even in the general population (17–19), has challenged this paradigm. Alternative mechanisms for low-level troponin release have therefore been proposed, including cardiomyocyte apoptosis and increased physiological cell turnover (20). These mechanisms could be relevant in the setting of increased myocardial strain (21,22) and increased LV mass and remodeling (17,23). In addition, a reversible increase in cell wall permeability to cardiac troponins or troponin fragments after short periods of myocardial ischemia (24) would be compatible with the chronic, low-grade elevations of cardiac troponins observed in patients with stable CAD and in those with chronic heart failure.

Table 5 Final Multivariable Cox Regressions Models for Cardiovascular Death or Congestive Heart Failure Dichotomized at Sex-Specific 99th Percentile of Healthy Subjects

Variable	>99th Percentile for hs-TnI and hs-TnT	
	HR (95% CI)	p
hs-TnI	1.96 (1.40–2.74)	<0.0001
hs-TnT	1.43 (1.00–2.05)	0.051
Age	1.04 (1.02–1.07)	<0.0001
LVEF < 50%	1.24 (0.90–1.70)	0.19
eGFR	1.00 (0.99–1.00)	0.36
Current smoking	1.62 (1.08–2.42)	0.019
History of hypertension	1.21 (0.89–1.65)	0.23
History of myocardial infarction	1.13 (0.82–1.55)	0.46
History of diabetes mellitus	1.75 (1.25–2.45)	0.001
History of CABG	1.55 (1.13–2.11)	0.006
Serum total cholesterol	1.00 (1.00–1.01)	0.089
History of intermittent claudication	1.72 (1.17–2.51)	0.005
Lipid-lowering therapy	0.69 (0.51–0.95)	0.020
ln NT-proBNP	1.52 (1.28–1.81)	<0.0001
ln CRP	1.04 (0.90–1.20)	0.60

Abbreviations as in Tables 1 to 3.

Although cTnI and cTnT display very similar serum profiles after acute ischemic injury and have been considered to provide largely interchangeable diagnostic and prognostic information in the setting of acute coronary syndromes (5), the 2 have differing biological characteristics that may be of clinical relevance in the ambulatory setting, where chronic rather than acute injury is responsible for troponin release. Although we observed that hs-TnT and hs-TnI shared several determinants, the strength of associations differed somewhat for many of these factors. For instance, the impact of prior AMI appeared to play a more important role for circulating hs-TnI levels than for hs-TnT levels. In contrast, the impact of renal function, age, and sex appeared to be slightly stronger for hs-TnT than for hs-TnI.

Several factors may contribute to these differences in distribution patterns. First, the molecular size of troponin I (24 kDa) is smaller than that of troponin T (37 kDa), which may facilitate transfer of troponin I or troponin I fragments across the viable cell membrane. Moreover, the degradation mechanisms may differ (16). For instance, in patients with renal failure, the association with LV mass may be stronger for troponin T than for troponin I (25). We have previously reported that cTnI may increase in proportion to the severity of myocardial ischemia (8), whereas no such association was evident for cTnT in a similar study (7). These differences suggest that although both hs-TnI and hs-TnT are markers of subclinical cardiac injury, they may reflect subtle differences in the etiology of cardiac injury and clearance

Table 6 Risk Associated With Concordant or Discordant Levels of hs-TnI and hs-TnT

Variable	n	Cardiovascular Death or Heart Failure		Myocardial Infarction	
		HR (95% CI)	p	HR (95% CI)	p
hs-TnI low and hs-TnT low (reference category)	942				
(hs-TnI high and hs-TnT low) or (hs-TnI low and hs-TnT high)	1,047	2.25 (1.18–4.28)	0.014	0.96 (0.66–1.39)	0.819
hs-TnI high and hs-TnT high	1,509	7.57 (4.30–13.35)	<0.001	1.10 (0.79–1.55)	0.572

"High" defined as greater or equal to the sex-specific 75th percentile of healthy subjects (hs-TnI: 4.2 pg/ml in men, 2.8 pg/ml in women; hs-TnT: 5.6 pg/ml in men, 3.9 pg/ml in women). "Low" defined as lower than the sex-specific 75th percentile of healthy subjects.

Abbreviations as in Tables 1 to 3.

mechanisms from the circulation. As such, they may be complementary rather than redundant biomarkers.

Prognostic value of hs-TnI and hs-TnT in patients with stable CAD. The finding that hs-TnI and hs-TnT display slightly different patterns of distribution and determinants not only suggests that biological differences may exist but raises the questions of whether hs-TnI and hs-TnT may have different diagnostic and prognostic properties. The observation that hs-TnI is increased above the 99th percentile in a lower percent of patients with stable CAD than hs-TnT may have diagnostic implications; that is, the signal-to-noise ratio may differ between the 2 with regard to the detection of acute ischemic myocardial injury. Moreover, the finding that hs-TnI, but not hs-TnT, was independently associated with the incidence of AMI may also reflect biological differences that translate into different prognostic properties. The exact mechanism underlying the association between hs-TnI and the incidence of AMI remains unknown. Recent computed tomographic angiographic data demonstrating higher troponin levels in patients with remodeled, noncalcified plaques are compatible with the idea that chronic but clinically silent rupture of atherosclerotic plaques may cause microembolization that may be a source of chronic troponin elevation (26). Moreover, as patients with remodeled, noncalcified plaques are thought to be those at highest risk for future plaque rupture, this may provide a rationale for the association between hs-TnI and the risk for future AMI. However, it remains unclear why such a mechanisms would preferentially involve hs-TnI, and the finding requires confirmation in other study cohorts.

A strong association between chronic circulating concentrations of hs-TnT and the incidence of cardiovascular death or congestive heart failure was first reported in patients with stable CAD (4) and subsequently confirmed in several large, population-based studies (17–19). Moreover, the Heart Outcomes Prevention Evaluation investigators recently reported an association between hs-TnI levels and the risk for cardiovascular events in a high-risk population (9). The present study extends this information by showing that both hs-TnI and hs-TnT provide strong and independent prognostic information for the endpoints of cardiovascular death or congestive heart failure, underscoring that chronic, low-grade injury may represent an intermediate phenotype in the pathway to congestive heart failure among at-risk patients. Future studies must identify therapeutic strategies that mitigate risk associated with these pathways.

Strengths and limitations. Strengths of the present investigation include the large sample size, long-term follow-up period, and large number of endpoints. Moreover, the prospective observational design of the PEACE biomarker study and the inclusion of both hs-TnI and hs-TnT in the same analysis represent strengths. A limitation of our study is that we cannot rule the possibility that part of the observed differences are due not to differing biological characteristics of cTnI and cTnT but rather to analytical differences between the assays. Along the same line of argument, our results cannot be extrapolated to other hs-TnI assays. It should also be noted that we used a pre-commercial version of the hs-TnT assay and that the results may deviate slightly from those obtained from the current commercial version. However, the main finding of our study, that hs-TnT and hs-TnI provide complementary prognostic information, is unlikely to have been influenced by the minor analytical differences between the pre-commercial and current versions of the assay.

Conclusions

In patients with stable CAD and preserved LV systolic function, concentrations of hs-TnI and hs-TnT are corre-

Table 7 C-Index and IDI: Effect of Adding hs-TnI and hs-TnT to Multivariate Models for Cardiovascular Death or Heart Failure

Variable	Dichotomous hs-TnI and hs-TnT				Continuous hs-TnI and hs-TnT			
	C-Index (95% CI)	p	IDI	p	C-Index (95% CI)	p	IDI	p
Multivariate model without hs-TnI or hs-TnT	0.763 (0.725–0.801)	NA			0.763 (0.725–0.801)	NA		
hs-TnI	0.777 (0.740–0.814)	0.046	0.010 (0.007–0.014)	<0.001	0.778 (0.741–0.814)	0.026	0.008 (0.005–0.012)	<0.001
hs-TnT	0.774 (0.737–0.811)	0.048	0.006 (0.003–0.009)	0.001	0.785 (0.749–0.821)	0.004	0.011 (0.007–0.014)	<0.001

IDI = integrated discrimination improvement; NA = not applicable. Other abbreviations as in Tables 1 to 3.

lated only moderately. hs-TnI concentrations are independently associated with the risk for cardiovascular death or heart failure and provide incremental prognostic information to conventional risk markers and other cardiovascular biomarkers, including hs-TnT. Notably, hs-TnI, but not hs-TnT, was significantly associated with the risk for AMI. Accordingly, chronic, low-grade elevation of hs-TnI and hs-TnT in patients with stable CAD may potentially reflect different pathophysiological determinants and suggest different therapeutic responses.

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REFERENCES

1. Thygesen K, Alpert JS, White HD, on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Circulation 2007;116:2634–53.
2. Anderson JL, Adams CD, Antman EM, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;123:e426–579.
3. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin Chem 2012;58:1574–81.
4. Omland T, de Lemos JA, Sabatine MS, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med 2009;361:2538–47.
5. Thygesen K, Mair J, Katus H, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J 2010;31:2197–204.
6. Reiter M, Twerenbold R, Reichlin T, et al. Early diagnosis of acute myocardial infarction in patients with pre-existing coronary artery disease using more sensitive cardiac troponin assays. Eur Heart J 2012;33:988–97.
7. Røysland R, Kravdal G, Høiseth AD, et al. Cardiac troponin T levels and exercise stress testing in patients with suspected coronary artery disease: the Akershus Cardiac Examination (ACE) 1 study. Clin Sci (Lond) 2012;122:599–606.
8. Sabatine MS, Morrow DA, de Lemos JA, Jarolim P, Braunwald E. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. Eur Heart J 2009;30:162–9.
9. Kavsak PA, Xu L, Yusuf S, McQueen MJ. High-sensitivity cardiac troponin I measurement for risk stratification in a stable high-risk population. Clin Chem 2011;57:1146–53.
10. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. N Engl J Med 2004;351:2058–68.
11. Omland T, Sabatine MS, Jablonski KA, et al. Prognostic value of B-Type natriuretic peptides in patients with stable coronary artery disease: the PEACE trial. J Am Coll Cardiol 2007;50:205–14.
12. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, for the Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461–70.
13. Shtatland E, Kleinman K, Cain EM. Model building in PROC PHREG with automatic variable selection and information criteria. Available at: http://www2.sas.com/proceedings/sugi30/206-30.pdf. Accessed January 15, 2013.
14. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med 2004;23:2109–23.
15. Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72.
16. McDonough JL, Van Eyk JE. Developing the next generation of cardiac markers: disease-induced modifications of troponin I. Prog Cardiovasc Dis 2004;47:207–16.
17. de Lemos JA, Drazner MH, Omland T, 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.
18. Defilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;2494–502.
19. Saunders JT, Nambi V, de Lemos JA, 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.
20. White HD. Pathobiology of troponin elevations: do elevations occur with myocardial ischemia as well as necrosis? J Am Coll Cardiol 2011;57:2406–8.
21. Hessel MH, Atsma DE, van der Valk EJ, et al. Release of cardiac troponin I from viable cardiomyocytes is mediated by integrin stimulation. Pflugers Arch 2008;455:979–86.
22. Feng J, Schaus BJ, Fallavollita JA, et al. Preload induces troponin I degradation independently of myocardial ischemia. Circulation 2001;103:2035–7.
23. Røsjø 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.
24. Labugger R, Organ L, Collier C, Atar D, Van Eyk JE. Extensive troponin I and T modification detected in serum from patients with acute myocardial infarction. Circulation 2000;102:1221–6.
25. Petrovic D, Obrenovic R, Stojimirovic B. Cardiac troponins and left ventricular hypertrophy in hemodialysis patients. Clin Lab 2008;54:145–52.
26. Korosoglou G, Lehrke S, Mueller D, et al. Determinants of troponin release in patients with stable coronary artery disease: insights from CT angiography characteristics of atherosclerotic plaque. Heart 2011;97:823–31.

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