Clinical Chemistry 64:9
1370–1379 (2018)

Cardiac Troponin T Concentrations, Reversible Myocardial Ischemia, and Indices of Left Ventricular Remodeling in Patients with Suspected Stable Angina Pectoris: a DOPPLER-CIP Substudy

Peder L. Myhre,[1,2] Torbjørn Omland,[1] Sebastian I. Sarvari,[3] Heikki Ukkonen,[4] Frank Rademakers,[5] Jan E. Engvall,[6] Tor-Arne Hagve,[7] Eike Nagel,[8] Rosa Sicari,[9] Jose L. Zamorano,[10] Mark Monaghan,[8] Jan D'hooge,[5] Thor Edvardsen,[3] and Helge Røsjø[1*] on behalf of the DOPPLER-CIP Study Group[†]

BACKGROUND: Cardiac troponin T concentrations measured with high-sensitivity assays (hs-cTnT) provide important prognostic information for patients with stable coronary artery disease (CAD). However, whether hs-cTnT concentrations mainly reflect left ventricular (LV) remodeling or recurrent myocardial ischemia in this population is not known.

METHODS: We measured hs-cTnT concentrations in 619 subjects with suspected stable CAD in a prospectively designed multicenter study. We identified associations with indices of LV remodeling, as assessed by cardiac MRI and echocardiography, and evidence of myocardial ischemia diagnosed by single positron emission computed tomography.

RESULTS: Median hs-cTnT concentration was 7.8 ng/L (interquartile range, 4.8–11.6 ng/L), and 111 patients (18%) had hs-cTnT concentrations above the upper reference limit (>14 ng/L). Patients with hs-cTnT >14 ng/L had increased LV mass (144 ± 40 g vs 116 ± 34 g; $P < 0.001$) and volume (179 ± 80 mL vs 158 ± 44 mL; $P = 0.006$), lower LV ejection fraction (LVEF) (59 ± 14 vs 62 ± 11; $P = 0.006$) and global longitudinal strain (14.1 ± 3.4% vs 16.9 ± 3.2%; $P < 0.001$), and more reversible perfusion defects ($P = 0.001$) and reversible wall motion abnormalities ($P = 0.008$). Age ($P = 0.009$), estimated glomerular filtration rate ($P = 0.01$), LV mass ($P = 0.003$), LVEF ($P = 0.03$), and evidence of reversible myocardial ischemia ($P = 0.004$ for perfusion defects and $P = 0.02$ for LV wall motion) were all associated with increasing hs-cTnT concentrations in multivariate analysis. We found analogous results when using the revised US upper reference limit of 19 ng/L.

CONCLUSIONS: hs-cTnT concentrations reflect both LV mass and reversible myocardial ischemia in patients with suspected stable CAD.

Patients with stable coronary artery disease (CAD)[11] have increased risk of death compared with individuals in the general population. Mechanisms of death relate to both new ischemic events and progressive left ventricular (LV) remodeling and heart failure (HF) development *(1)*. Cardiac troponin measurements with high-sensitivity (hs) assays have been found to improve risk prediction in patients with stable CAD *(2–4)*, but there is a need for

[1] Division of Medicine, Akershus University Hospital, Lørenskog, Norway and Center for Heart Failure Research, University of Oslo, Oslo, Norway; [2] Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [3] Department of Cardiology, Oslo University Hospital, Rikshospitalet and Center for Heart Failure Research, University of Oslo, Oslo, Norway; [4] Department of Medicine, Turku University Hospital, Turku, Finland; [5] Department of Cardiovascular Sciences, University Hospitals Leuven and KU Leuven, Leuven, Belgium; [6] Department of Clinical Physiology Linköping University, Linköping, Sweden and Center for Medical Image Science and Visualization (CMIV), Linköping University, Linköping, Sweden; [7] Division of Diagnostics and Technology, Akershus University Hospital, Lørenskog and Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [8] Kings College Hospital, Department of Non-invasive Cardiology, Denmark Hill, London, UK; [9] CNR, Istituto di Fisiologia Clinica, Pisa, Italy; [10] Hospital Universitario Ramón y Cajal, Cardiovascular Imaging Unit, Madrid, Spain.

* Address correspondence to this author at: Division of Medicine, Akershus University Hospital, Sykehusveien 25, 1478 Lørenskog, Norway. Fax +47-67962190; e-mail helge.rosjo@medisin.uio.no.

† A complete list of the investigators who participated to the study is presented in the Appendix to the online Data Supplement.

Received March 10, 2018; accepted June 1, 2018.
Previously published online at DOI: 10.1373/clinchem.2018.288894

[11] Nonstandard abbreviations: CAD, coronary artery disease; LV, left ventricular; HF, heart failure; hs-cTnT, high-sensitivity cardiac troponin T; DOPPLER-CIP, Determining Optimal noninvasive Parameters for the Prediction of Left vEntricular morphologic and functional Remodeling in Chronic Ischemic Patients; ECG, electrocardiogram; SPECT, single-positron emission computed tomography; CMR, cardiac magnetic resonance; GLS, global longitudinal strain; LA, left atrial; MPI, myocardial perfusion imaging; SSS, summed stress score; SDS, summed difference score; URL, upper reference limit; eGFR, estimated glomerular filtration rate.

clinical studies with extensive cardiovascular phenotyping to decipher the specific pathophysiology reflected by hs-troponin concentrations in patients with stable CAD.

Cardiac troponins I and T are important components of the contractile apparatus in cardiomyocytes. Measurement of cardiac troponins is a sine qua non criterion for diagnosing acute myocardial infarction in patients with chest pain *(5)*. With the introduction of hs-troponin assays, cardiac troponin concentrations can be reliably measured in the nonacute setting. In patients with stable CAD, hs-troponin concentrations primarily have been found to be more closely associated with cardiovascular death and HF hospitalizations than with myocardial infarctions *(3, 6)*. Strong associations with cardiovascular death and HF development have also been reported for hs-troponin measurements in the general population *(7–11)*; thus, hs-troponin concentrations seem to reflect progressive LV remodeling in patients with stable and subclinical cardiovascular disease *(12)*. Pertinent to this point, hs-troponin concentrations also correlate with LV mass in patients with aortic stenosis *(13, 14)* or hypertrophic cardiomyopathy *(15)* and in individuals from the general population *(9, 16, 17)*. Moreover, although there are conflicting results as to whether hs-troponin concentrations increase during exercise stress testing in patients with reversible myocardial ischemia, previous studies generally have reported increased steady-state hs-troponin concentrations in these patients *(18–22)*. Based on this lack of knowledge, there is a need for clinical studies with hs-troponin measurements and detailed phenotyping of the participants relating to both myocardial ischemia (stress-induced perfusion or wall motion abnormalities) and LV remodeling (mass, volume, function, and scarring). Accordingly, in this large multicenter study with multimodal state-of-the-art cardiac imaging at rest and during stress, we assessed whether hs-cardiac troponin T (hs-cTnT) concentrations primarily reflect LV mass or myocardial ischemia in patients with suspected stable CAD.

Methods

STUDY DESIGN AND POPULATION

The Determining Optimal noninvasive Parameters for the Prediction of Left vEntricular morphologic and functional Remodeling in Chronic Ischemic Patients (DOPPLER-CIP) Study was performed in 10 centers from 7 European countries and was designed to investigate different noninvasive parameters for the prediction of LV morphologic and functional remodeling in patients with stable CAD *(23)*. Between February 2010 and December 2012, 676 patients met the inclusion criteria of suspected ongoing myocardial ischemia defined as (*a*) history of typical or atypical angina, (*b*) high risk of coronary disease (>15% risk of cardiovascular events according to the European Systematic Coronary Risk Evaluation) *(24)*, or (*c*) positive stress testing according to criteria at the individual site. Patients with acute coronary events during the past 3 months, life expectancy <2 years, more than moderate valvular heart disease, pacemaker with predominant pacing rhythm, or permanent atrial fibrillation were excluded. Demographic data and medical history were collected, and all patients underwent standard diagnostic testing, including vital parameters, electrocardiogram (ECG), and resting echocardiographic examination. Patients were required to complete at least 2 of the following functional imaging modalities to be included into the DOPPLER-CIP study: nuclear imaging [single-positron emission computed tomography (SPECT)], cardiac magnetic resonance (CMR) imaging, or stress echocardiography. Quantitative measures were performed in dedicated core laboratory facilities by analysts blinded to patient information, results from other imaging modalities, and biomarker concentrations. After excluding 21 patients with missing or noninterpretable results from SPECT, CMR, or echocardiography, 619 patients (92% of the total population) with available hs-cTnT measurements were included in the current study (Fig. 1). Patients were required to give informed consent before inclusion, and the study was approved by the ethics committees at the different sites.

Fig. 1. Breakdown of the available measurements.
The number of patients with suspected CAD who had available measurements from echocardiography, MPI-SPECT, CMR, and MPI-MRI in the DOPPLER-CIP biomarker substudy on hs-cTnT.

CARDIAC IMAGING

Echocardiography. The echocardiography recordings (n = 571; 92%) were acquired by a standardized imaging protocol using Philips (iE33), GE (Vivid 7 or e9), or Siemens (Sequoia). All recordings contained at least 3 consecutive heart cycles during breath-holding when feasible. LV systolic function was assessed by LV ejection fraction and global longitudinal strain (GLS). LV diastolic function was assessed based on left atrial (LA) volume, peak early diastolic myocardial tissue velocity measured from the mitral annulus by tissue Doppler imaging (e'), and the ratio between early diastolic velocity in transmitral Doppler (E) and e' (E/e').

Cine CMR. Resting CMR cine imaging (n = 339; 55%) was performed with the patient in the supine position in short axis, 2-chamber, and 4-chamber orientations with an optional short axis left atrium cine *(25)*. All examinations were performed at 1.5 T using Philips Achieva in 3 sites and Siemens Sonata in 1 site following an established protocol *(26)*. Recordings were done in 3 or 2 dimensions during breath-holding, in-plane resolution $<$1.5 mm, slice thickness of 6 to 8 mm with 2- to 4-mm interslice gaps to equal 10 mm, temporal resolution $<$45 ms between phases, and parallel imaging if available. Late gadolinium enhancement was used to assess myocardial scarring.

Nuclear imaging. SPECT (n = 430; 67%) acquisition and processing were performed in accordance with the European Association of Nuclear Medicine/European Society of Cardiology procedural guidelines for myocardial perfusion imaging in nuclear cardiology *(27)*. Of the patients who underwent SPECT, 256 patients (60%) also had CMR cine images available. Preferably, patients were examined with either an exercise stress test and single-day rest–stress myocardial perfusion imaging (MPI) or a 2-day protocol. Patients who could not undergo exercise stress followed a pharmacologic stress protocol. Myocardial perfusion in each of the 17 segments was classified according to established methods to calculate summed stress score (SSS; $\geq$4 pathological) and summed difference score (SDS; $\geq$2 considered indicative of reversible perfusion defects) *(28)*. Regional wall motion analysis was also classified according to established methods to calculate the SSS for wall motion ($\geq$4 pathological) and the SDS for wall motion ($\geq$3 considered indicative of reversible hypokinesis) *(29)*. Details of the nuclear imaging protocol are reported in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol64/issue9.

Perfusion MRI. Adenosine stress perfusion MRI was conducted in 210 patients (33%) (see online Data Supplement for detailed protocol).

BLOOD SAMPLING AND TROPONIN MEASUREMENTS

Blood samples were collected by venipuncture into chilled heparinized tubes. The samples were immediately centrifuged at 4 °C, and the plasma was pipetted and frozen initially at −20 °C. The samples were later stored at −80 °C before transportation to Akershus University Hospital for analysis. Troponin T was analyzed with a commercially available hs assay (Elecsys TnT hs STAT, Roche Diagnostics). The limit of the blank was 3.0 ng/L, and the analytical range was 3 to 10 000 ng/L *(30)*. The CVs in our laboratory were 4.6% and 2.3% in the low range (hs-cTnT, 4 and 8 ng/L, respectively; n = 10) and 3.5% and 2.8% in the high range (hs-cTnT, 25 and 1200 ng/L, respectively; n $>$24). Samples with undetectable concentrations of hs-cTnT were set to 3.0 ng/L by convention.

STATISTICAL ANALYSIS

Continuous variables are presented as mean (SD) or median (quartile, 1–3) for nonparametric variables. Categorical variables are presented as absolute numbers and percentages. The patients were stratified according to the hs-cTnT upper reference limit (URL) of 14 ng/L *(31, 32)*, sex-specific cutoffs (8.9 ng/L for women and 15.5 ng/L for men) *(31)*, and the recently implemented US URL (19 ng/L) *(33, 34)*. Statistical comparisons were made with the Pearson χ^2 test for categorical variables, 1-way ANOVA for parametric continuous variables, and the Kruskal–Willis test for nonparametric continuous variables. Correlations were calculated by Spearman rank correlation. To assess the variables associated with high troponin concentrations, we performed multivariable linear regression with troponin as the dependent variable in 2 separate models. Model 1 was a demographic and clinical model that included age, sex, body mass index, mean arterial blood pressure, heart rate, comorbidities (diabetes, previous myocardial infarction, or previous coronary revascularization), and estimated glomerular filtration rate (eGFR), calculated by the chronic kidney disease epidemiology collaboration equation *(35)*. Model 2 included all the variables from model 1 plus measurements of LV structure and function by CMR (mass, ejection fraction, and scar), measurements of systolic and diastolic function by echocardiography (GLS, e', E/e', and LA volume), and measurements of myocardial perfusion and wall motion assessed by SPECT during stress (SSS and SSS for wall motion) and difference from rest to stress (SDS and SDS for wall motion). The results from the SPECT test were dichotomized according to cutoffs specified above and included in separate multivariable models because of collinearity between SSS, SDS, SSS for wall motion, and SDS for wall motion. The ratio of the effect estimates is presented with 95% CI. hs-cTnT concentrations were transformed by the natural logarithm before all regression analysis

Table 1. Baseline characteristics of stable patients with suspected CAD stratified according to hs-cTnT URL.

	hs-cTnT− ≤14 ng/L (n = 508)	hs-cTnT+ >14 ng/L (n = 111)	*P* value
Age, year	62.9 ± 8.6	68.7 ± 9.0	<0.001
Sex, female	141 (27.8%)	12 (10.8%)	<0.001
Body mass index, kg/m^2	27.5 ± 3.9	28.1 ± 3.8	0.18
Tobacco smoking	86 (17.0%)	13 (11.8%)	0.18
Mean arterial blood pressure, mmHg	98 ± 12	98 ± 12	0.89
Heart rate, beats/min	68 ± 13	68 ± 12	0.95
NYHA[a] class 3 or 4	59 (11.6%)	17 (15.3%)	0.28
Left ventricular hypertrophy in ECG	20 (4.0%)	5 (4.5%)	0.80
QRS width in ECG, ms	94 ± 16	101 ± 24	<0.001
History			
Diabetes mellitus	81 (16.0%)	35 (31.8%)	<0.001
Hypertension	292 (57.7%)	79 (71.8%)	0.006
Myocardial infarction	222 (43.9%)	62 (56.4%)	0.017
Coronary revascularization	249 (49.0%)	64 (57.7%)	0.10
Medications			
ACE-i[b]/ARB[c]	258 (51.3%)	69 (62.7%)	0.029
Nitrates	134 (26.5%)	41 (36.9%)	0.028
Aspirin	410 (81.2%)	96 (86.5%)	0.19
Statins	396 (78.4%)	91 (82.0%)	0.40
Hemoglobin, g/dL	143.8 ± 12.4	139.4 ± 13.6	<0.001
White blood cell count, ×10^9/L	5.6 ± 0.9	6.1 ± 1.1	<0.001
Hemoglobin A1c, %	7.0 ± 2.0	7.5 ± 2.3	0.014
LDL cholesterol, mmol/L	2.5 ± 0.9	2.3 ± 1.0	0.049
eGFR, mL/min/1.73 m^2	83.7 ± 15.2	72.5 ± 16.6	<0.001

[a] New York Heart Association.
[b] Angiotensin-converting enzyme inhibitor.
[c] Angiotensin receptor blocker.

because of a right-skewed distribution. We also performed 2 sensitivity analyses: (*a*) using results from MRI-MPI to validate results from SPECT-MPI (model 2B) and (*b*) using echocardiographic measures of LV mass and LV ejection fraction to validate the results from cine CMR (model 2C). All statistical tests were 2-sided using a type I error threshold of 0.05. The statistical analyses were performed with IBM® SPSS® Statistics version 22 for Windows.

Results

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS AND hs-cTnT CONCENTRATIONS

The median hs-cTnT concentration in the cohort was 7.8 ng/L (interquartile range, 4.8–11.6 ng/L), and 111 patients (18%) had hs-cTnT concentrations above the 99th percentile. Demographic and clinical characteristics with patients stratified according to concentrations of hs-cTnT above (hs-cTnT+) or below (hs-cTnT−) the URL are presented in Table 1. hs-cTnT+ patients were older; more often men; had higher prevalence of diabetes mellitus, hypertension, and previous myocardial infarction; wider QRS-complexes on ECG; and used more angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and nitrates. Also, hs-cTnT+ patients had higher HbA1c and lower eGFR, hemoglobin, and LDL cholesterol compared with hs-cTnT− patients.

hs-cTnT concentrations correlated with several demographical and clinical variables, including eGFR ($r = -0.29$; $P < 0.001$), sex ($r = 0.35$; $P < 0.001$), and age ($r = 0.34$; $P < 0.001$) (see Table 1 in the online Data Supplement). In a multivariable linear regression analysis that included demographic and clinical variables, age ($P < 0.001$), male sex ($P < 0.001$), body mass index ($P = 0.003$), history of diabetes mellitus ($P = 0.01$),

history of myocardial infarction ($P = 0.008$), and eGFR ($P < 0.001$) were all associated with increasing hs-cTnT concentrations (Table 2, multivariate model 1).

LV STRUCTURAL AND FUNCTIONAL STATUS AND hs-cTnT CONCENTRATIONS

Compared with hs-cTnT− patients, hs-cTnT+ patients had higher LV mass and LV end-diastolic volume and lower LV ejection fraction and GLS (Table 3). In contrast, hs-cTnT− and hs-cTnT+ patients did not differ regarding LV scar burden, LA volume, e', or E/e' ratio. Of the investigated imaging parameters at rest, we found significant correlations between hs-cTnT and LV mass ($r = 0.40$; $P < 0.001$), LV scar burden ($r = 0.33$; $P < 0.001$), LV end-diastolic volume ($r = 0.28$; $P < 0.001$), LV ejection fraction ($r = -0.25$; $P < 0.001$), and GLS ($r = 0.21$; $P < 0.001$) (see Table 1 in the online Data Supplement). The relation between hs-cTnT and LV mass was linear, and no interaction was observed for sex ($P = 0.96$) (Fig. 2A, left panel).

INDICES OF MYOCARDIAL ISCHEMIA AND hs-cTnT CONCENTRATIONS

hs-cTnT+ patients had more perfusion defects and hypokinesis during stress compared with hs-cTnT− patients (Table 3). There were also differences in reversible perfusion defects and reversible hypokinesis between the groups (Table 3). Stratifying patients also according to sex-specific cutoffs (8.9 ng/L for women and 15.5 ng/L for men) and to the recently proposed US upper reference concentration of 19 ng/L yielded similar results as found using 14 ng/L as the cutoff (see Tables 2 and 3 in the online Data Supplement). hs-cTnT correlated with perfusion defects and hypokinesis during stress ($r = 0.32$; $P < 0.001$ and $r = 0.36$; $P < 0.001$, respectively) and with the difference from rest to stress ($r = 0.23$; $P < 0.001$ and $r = 0.15$; $P = 0.002$, respectively) (see Table 3 in the online Data Supplement). The relation between hs-cTnT and reversible perfusion defects was linear ($P < 0.001$) and with no interaction by sex ($P = 0.57$) (see Fig. 2A, right panel).

MULTIVARIATE ASSESSMENT OF ANATOMIC AND FUNCTIONAL IMAGING AND hs-cTnT CONCENTRATIONS

To identify independent associations between hs-cTnT concentrations and imaging results from both anatomic and functional testing, we performed multivariable linear regression analysis in patients with both SPECT-MPI and cine CMR available (n = 256; 60% of the patients with SPECT-MPI data). In addition to age ($P < 0.001$) and eGFR ($P = 0.01$), LV mass ($P = 0.003$), LV ejection fraction ($P = 0.03$), and reversible perfusion defects ($P = 0.004$) were all independently associated with higher hs-cTnT concentrations (Table 2, multivariate model 2), and this model explained 48% of the variation in hs-cTnT concentrations ($r^2 = 0.48$). Reversible hypokinesia ($P = 0.02$) and hypokinesia during stress ($P = 0.002$) were also independently associated with higher hs-cTnT when replacing reversible perfusion defects in the same multivariable model (Table 2, multivariate model 2). In contrast, perfusion defects during stress, LV end-diastolic volume, LV scar burden, GLS, LA volume, e', and E/e' were not associated with hs-cTnT concentrations in the multivariable model. The results were similar when excluding participants with New York Heart Association class III or IV (see Table 4 in the online Data Supplement). The individual contribution of reversible perfusion defects and LV mass to increasing concentrations of hs-cTnT is illustrated in Fig. 2B.

We performed a sensitivity analysis in the subgroup of patients subjected to MRI-MPI (n = 210) to validate the association between hs-cTnT and reversible ischemia found with SPECT-MPI. The results from MRI-MPI stratified by European cutoffs, sex-specific cutoffs, and US cutoffs of hs-cTnT were comparable with results from SPECT-MPI (see Table 5 in the online Data Supplement). hs-cTnT concentrations correlated with perfusion defects during stress ($r = 0.33$; $P < 0.001$) and reversible perfusion defects ($r = 0.28$; $P < 0.001$) as determined by MRI-MPI (see Table 1 in the online Data Supplement). Like the results for SPECT-MPI, more reversible perfusion defects by MRI-MPI during stress and difference from rest to stress were associated with higher hs-cTnT in multivariable regression models ($P = 0.005$ and $P = 0.001$, respectively) (see Table 6 in the online Data Supplement, multivariable model 2B). In total, 169 patients had results from both SPECT-MPI and MRI-MPI, and the correlation coefficient during stress for the 2 modalities was $r = 0.42$ ($P < 0.001$).

We also recalculated the multivariable model 2 with echocardiographic (as opposed to CMR-derived) measurements for LV ejection fraction and mass (n = 341, which included 79% of the patients with SPECT-MPI results) (see Table 7 in the online Data Supplement, multivariable model 2C). In line with the results using CMR-derived data, age ($P < 0.001$), sex ($P < 0.001$), eGFR ($P = 0.03$), LV mass ($P < 0.001$), LV ejection fraction ($P = 0.007$), and reversible perfusion defects ($P = 0.003$) were all associated with increasing hs-cTnT concentrations in the multivariable model based on echocardiographic measurements. Reversible hypokinesia ($P < 0.001$) and hypokinesia during stress ($P = 0.002$), but not perfusion defects during stress, were also associated with increasing hs-cTnT concentrations when using echocardiography-derived measurements (see Table 7 in the online Data Supplement, multivariable model 2C).

Table 2. Predictors of higher concentrations of hs-cTnT (log-transformed) assessed by linear regression.[a]

	Univariate			Multivariate model 1 (adjusted R^2 for model = 0.29)			Multivariate model 2 (adjusted R^2 for model = 0.48)			
	Ratio of effect estimates (95% CI)	T	*P* value	Ratio of effect estimates (95% CI)	T	*P* value	Ratio of effect estimates (95% CI)	T	*P* value	R^2, %
Age, per year	1.03 (1.02–1.03)	9.1	<0.001	1.02 (1.02–1.03)	6.8	<0.001	1.02 (1.01–1.04)	2.7	0.009	2.1
Female sex	0.61 (0.54–0.68)	8.6	<0.001	0.64 (0.57–0.71)	8.0	<0.001			NS[b]	0.9
Body mass index, per kg/m^2	1.02 (1.00–1.03)	2.5	0.01	1.02 (1.01–1.03)	3.0	0.003			NS	0
Tobacco smoking	0.91 (0.79–1.05)	1.4	0.18			NS			NS	0
MAP[c], per mmHg	1.00 (1.00–1.01)	0.5	0.62			NS			NS	0
Heart rate, beats/min	1.00 (0.99–1.00)	1.9	0.06			NS			NS	0
Diabetes	1.35 (1.19–1.54)	4.5	<0.001	1.17 (1.03–1.32)	2.5	0.01			NS	0.5
Hypertension	1.25 (1.12–1.39)	4.1	<0.001			NS			NS	0.3
Previous myocardial Infarction	1.27 (1.14–1.40)	4.5	<0.001	1.17 (1.04–1.31)	2.7	0.008			NS	0
Previous coronary revascularization	1.23 (1.11–1.37)	3.9	<0.001			NS			NS	0
eGFR, per mL/min/1.73 m^2	0.99 (0.98–0.99)	7.7	<0.001	0.99 (0.99–1.00)	3.9	<0.001	0.99 (0.98–1.00)	3.9	0.01	2.9
CMR LV mass, per g	1.01 (1.01–1.01)	8.7	<0.001				1.01 (1.00–1.01)	3.1	0.003	4.9
CMR LV end diastolic volume, per mL	1.00 (1.00–1.01)	7.1	<0.001						NS	0
CMR LV ejection fraction, per %	0.98 (0.98–0.99)	5.1	<0.001				0.99 (0.97–1.00)	2.2	0.03	2.2
CMR LGE[d] scar, per %	1.02 (1.01–1.03)	3.2	0.002						NS	0.3
Echo[e] GLS, per %	1.08 (1.06–1.10)	7.2	<0.001						NS	0
Echo left atrial volume, per mL	1.01 (1.01–1.02)	3.4	0.001						NS	0
Echo TDI[f] e', per m/s	0.94 (0.92–0.97)	4.4	<0.001						NS	0
Echo E/e' ratio, per unit	1.02 (1.20–1.59)	4.6	0.007						NS	0.3
Reversible perfusion defects	1.38 (1.20–1.59)	4.6	<0.001				1.38 (1.11–1.72)	2.9	0.004	2.1
Perfusion defects during stress[g]	1.53 (1.31–1.80)	5.8	<0.001						NS	0.1
Reversible hypokinesis[g]	1.53 (1.31–1.80)	5.3	<0.001				1.36 (1.06–1.75)	2.4	0.02	1.8
Hypokinesis during stress[g]	1.59 (1.40–1.81)	7.0	<0.001				1.45 (1.14–1.84)	3.1	0.002	3.0

[a] Multivariable model 1 includes demographic and clinical variables in the total cohort. Model 2 also includes cardiac imaging in the patients with these variables available.
[b] Not significant.
[c] Mean arterial blood pressure.
[d] Echocardiography.
[e] Late gadolinium enhancement.
[f] Tissue Doppler imaging.
[g] Analyzed in separate multivariate models because of collinearity with reversible perfusion defects. Troponin was transformed by natural logarithm.

Table 3. Results of anatomic and functional cardiac imaging stratified according to hs-cTnT URL.

	hs-cTnT− (≤14 ng/L)	hs-cTnT+ (>14 ng/L)	*P* value
Anatomic imaging			
CMR LV mass, g	116 ± 34[a]	144 ± 40	<0.001
CMR LVEDV[b], mL	158 ± 44	179 ± 80	0.006
CMR LVEF[c], %	62 ± 11	59 ± 14	0.033
CMR LGE[d] scar, %	3.3 ± 6.2	4.2 ± 6.3	0.28
Echocardiography GLS, %	−17.1 ± 3.1	−15.0 ± 3.3	<0.001
Echocardiography LA volume, mL	40 ± 8	42 ± 8	0.09
Echocardiography TDI[e] e', cm/s	7.7 ± 2.3	7.2 ± 2.2	0.07
Echocardiography E/e' ratio	9.7 ± 4.2	10.6 ± 3.5	0.05
Functional stress imaging			
SPECT perfusion defects, stress	1 [0, 5]	6 [2, 10]	<0.001
SPECT perfusion defects, reversible	0 [0, 2]	1 [0, 4]	0.001
SPECT wall motion, stress	0 [0, 6]	7 [0, 21]	<0.001
SPECT wall motion, reversible	0 [0, 0]	0 [0, 4]	0.008

[a] Presented as mean ± SD and median (quartile 1, quartile 3).
[b] Left ventricular end diastolic volume.
[c] Left ventricular ejection fraction.
[d] Late gadolinium enhancement.
[e] Tissue Doppler imaging.

Discussion

The principal finding of our study is that hs-cTnT concentrations seem to integrate information on LV mass and myocardial ischemia in unselected patients with suspected CAD. The coherent results from both SPECT-MPI and MRI-MPI in our population support the validity of our findings.

The introduction of hs assays has provided an opportunity to investigate differences in cardiac troponin concentrations in patients without acute coronary syndrome. The association between increased troponin concentrations and future risk in patients with stable CAD is now well established *(36)*. However, to help guide therapy, more detailed information is needed on the underlying pathophysiology of hs-troponin increases in this and other patient groups with stable disease. Troponins are part of the contractile apparatus of cardiomyocytes, and large amounts of free troponin are rapidly released from pools in the cytoplasm during myocardial necrosis, i.e., during a myocardial infarction *(5)*. In addition, small quantities of free troponin are released in stable patients, and different mechanisms have been proposed *(37)*. Coronary artery plaques with small ruptures and subsequent microinfarctions could potentially contribute to troponin leakage in patients with stable CAD, as associations between hs-cTnT concentrations and plaque characteristics, but not stenosis severity grade, have been reported *(38)*. Patients with remodeled coronary artery plaques were also reported to have higher hs-cTnT concentrations compared with patients with coronary artery calcifications and open vessels. We and other groups have also previously demonstrated increased steady-state hs-troponin concentrations in individuals with reversible myocardial ischemia compared with those without reversible myocardial ischemia *(18–22)*. In contrast, whether the increment in hs-troponin concentrations is directly related to reversible myocardial ischemia has not been unequivocally established, as reversible ischemia was not retained in statistical multivariate models that adjusted for other differences between the groups *(21)*. Previous studies have also found divergent results relating to the effect of exercise stress testing on hs-troponin release *(18, 19, 21, 22, 39)*, and it appears that hs-cTnT concentrations increase during atrial pacing, irrespective of the presence or absence of reversible myocardial ischemia *(20)*. Hence, there are several controversies in the literature related to the association between reversible myocardial ischemia and hs-troponin concentrations.

In the current study, we add to the existing knowledge by providing additional data on the associations between hs-cTnT concentrations and indices of myocardial ischemia and LV remodeling in a large cohort of extensively phenotyped patients with suspected CAD. We found hs-cTnT concentrations to reflect both cardiac remodeling and reversible ischemia, including in com-

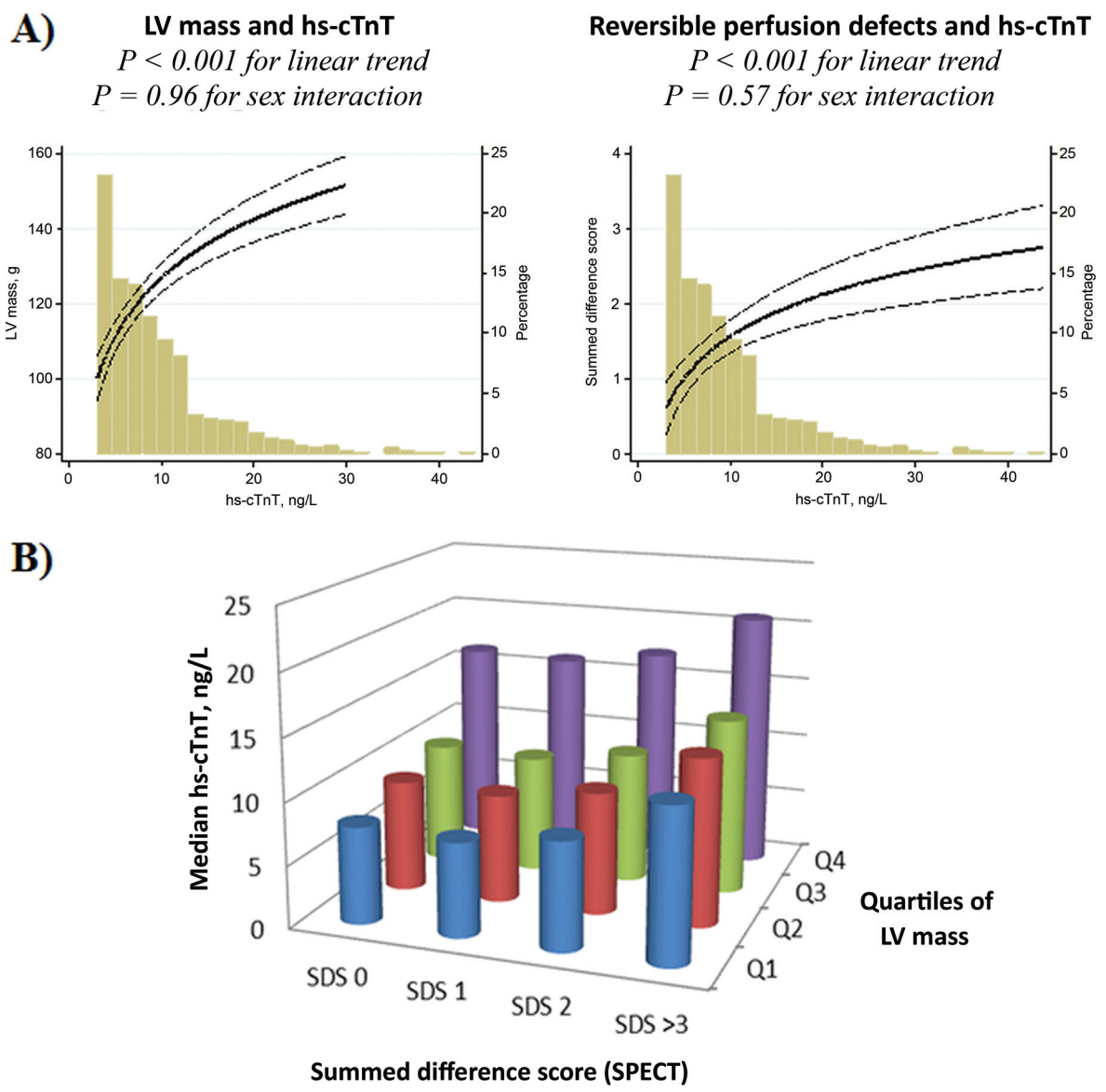

Fig. 2. The relation between hs-cTnT and LV mass and the relation between hs-cTnT and reversible perfusion defects (A), plus the contribution of reversible perfusion defects and LV mass to increasing concentrations of hs-cTnT (B).

(A), Fitted restricted cubic spline models of log-transformed hs-cTnT concentration and measurements of LV mass assessed by CMR (left) and SDS assessed by SPECT-MPI (right). (B), Median concentrations of hs-cTnT according to quartiles of LV mass and difference in myocardial perfusion defects from rest to stress (SDS).

prehensive statistical multivariate models that adjusted for many clinical, biochemical, and imaging variables. Hence, our results support the need for physicians to explore both CAD and subclinical HF as cause for increased hs-cTnT concentration in patients with symptoms of stable CAD. The finding that increasing hs-troponin is robustly associated with increasing LV mass is in line with previous data from other patient groups when hs-troponin concentrations reflected LV mass in patients with moderate to severe aortic stenosis *(13, 14)*, hypertrophic cardiomyopathy *(15)*, and Fabry disease *(40)*. We also found modest associations between increased troponin concentrations and parameters of cardiac function in our cohort, which suggest that hs-cTnT is an early marker of LV mass but not an accurate biomarker of systolic and diastolic LV impairment in pa-

tients with suspected CAD. This result is also analogous to previous data reported for patients with aortic stenosis and hypertrophic cardiomyopathy *(13–15)*. Of note, our model could explain only 48% of the variation on concentrations of hs-cTnT. Hence, there are still important contributors to circulating concentrations that are not accounted for by the clinical, biochemical, and imaging variables that were assessed in our patients.

This study has some strengths and limitations. The multicenter design and multimodal imaging with characterization of both LV remodeling and myocardial ischemia are strengths of this study. The moderate overlap of imaging modalities investigated in this study is a major limitation of this study. The reason for this is that clinical indication and local resources were considered when selecting modalities in the DOPPLER-CIP study *(23)*. We have tried to compensate for this limitation by performing a sensitivity analysis with echocardiographic variables of LV mass and LV ejection fraction (79% of patients with SPECT), and we found similar results as with CMR-based imaging, which is generally considered the most sensitive imaging modality for structural changes in the myocardium. The study also lacks information on which of the inclusion criteria led to individual patients being enrolled (angina pectoris, high risk by the European Systematic Coronary Risk Evaluation, or positive exercise stress testing). However, we believe our cohort represents a real-life population of patients with suspected myocardial ischemia based on the findings from myocardial perfusion imaging, the prevalence of comorbidities, and demographic variables. Finally, we lack data from invasive coronary angiography, which is a limitation for the classification of patients with stable CAD and for assessment of severity of obstructive coronary artery disease. Still, as we have data from several complementary modalities to determine functional reversible myocardial ischemia, including MRI-MPI, our results should still be valid despite the lack of anatomical information on coronary artery status.

Conclusion

We found that reversible ischemia and increased LV mass were independently associated with increased hs-cTnT concentrations in patients with suspected stable CAD. The association with reversible ischemia was consistent when examining myocardial perfusion and wall motion assessed by SPECT-MPI and validated using MRI-MPI.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

P.L. Myhre, statistical analysis; T. Omland, financial support; H. Ukkonen, provision of study material or patients; F. Rademakers, provision of study material or patients; J.E. Engvall, provision of study material or patients; J. Zamorano, provision of study material or patients; M. Monaghan, provision of study material or patients; T. Edvardsen, administrative support; H. Røsjø, financial support, statistical analysis.

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: T. Omland, Roche Diagnostics.
Stock Ownership: None declared.
Honoraria: P.L. Myhre, Novartis; T. Omland, Roche Diagnostics; E. Nagel, Bayer AG; M. Monaghan, Philips Medical Systems; H. Røsjø, Novartis.
Research Funding: This substudy was funded by Akershus University Hospital, the Norwegian Research Council, and the South-Eastern Regional Health Authority. The DOPPLER-CIP Study was funded by the EU (FP7) framework program. Roche Diagnostics (Penzberg, Germany) provided kits for hs-cTnT measurements at a reduced price. P.L. Myhre, a postdoctoral research grant from the South-Eastern Norway Regional Health Authority to Dr. Røsjø; T. Omland, Roche Diagnostics; M. Monaghan, research fees for acting as 3D Echo Core Lab.
Expert Testimony: None declared.
Patents: None declared.
Other Remuneration: E. Nagel, Bayer AG, Siemens Healthineers; J. Zamorano, Pfizer.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or final approval of manuscript.

Acknowledgements: The authors thank the Department of Clinical Biochemistry, Akershus University Hospital for the hs-cTnT analysis and the Clinical Trial Unit, Division of Medicine, Akershus University Hospital for coordination. The authors also thank the following individuals in the DOPPLER-CIP Study for their valuable contributions: Juhani Knuuti (Turku), Vitantonio Di Bello (Pisa), Covadonga Fernandez-Golfin (Madrid), Michelle Andrews (KCH, London), Peter Pearson (KCH, London), Tino Ebbers (Linköping), Gunborg Gidby (Linköping), Johan Kihlberg (Linköping), Henrik Haraldsson (Linköping), Margareth P. Ribe (Oslo), Valentina Puntmann (KCL, London), Jens-Uwe Voigt (Leuven), Lieven Herbots (Leuven), Piet Claus (Leuven), Kaatje Goetschalckx (Leuven), Ruta Jasaityte (Leuven), Valérie Robesyn (Leuven), and Ann Belmans (Leuven), as well as the EU (FP7) framework program for the financial support of this project. The authors thank AMID, Philips, GE, TomTec, and Medviso AB for their cooperation in this project by providing and developing software.

References

1. Roberts WC, Potkin BN, Solus DE, Reddy SG. Mode of death, frequency of healed and acute myocardial infarction, number of major epicardial coronary arteries severely narrowed by atherosclerotic plaque, and heart weight in fatal atherosclerotic coronary artery disease: analysis of 889 patients studied at necropsy. J Am Coll Cardiol 1990;15:196–203.

2. Lindholm D, Lindbäck J, Armstrong PW, Budaj A, Cannon CP, Granger CB, et al. Biomarker-based risk

model to predict cardiovascular mortality in patients with stable coronary disease. J Am Coll Cardiol 2017; 70:813–26.
3. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med 2009;361:2538–47.
4. Omland T, Pfeffer MA, Solomon SD, de Lemos JA, Rosjo H, Saltyte Benth J, et al. Prognostic value of cardiac troponin I measured with a highly sensitive assay in patients with stable coronary artery disease. J Am Coll Cardiol 2013;61:1240–9.
5. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35.
6. McQueen MJ, Kavsak PA, Xu L, Shestakovska O, Yusuf S. Predicting myocardial infarction and other serious cardiac outcomes using high-sensitivity cardiac troponin T in a high-risk stable population. Clin Biochem 2013;46: 5–9.
7. Daniels LB, Laughlin GA, Clopton P, Maisel AS, Barrett-Connor E. Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. J Am Coll Cardiol 2008;52:450–9.
8. Zethelius B, Johnston N, Venge P. Troponin I as a predictor of coronary heart disease and mortality in 70-year-old men: a community-based cohort study. Circulation 2006;113:1071–8.
9. 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.
10. 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.
11. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, Seliger SL. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;304:2494–502.
12. Omland T, Rosjo H, Giannitsis E, Agewall S. Troponins in heart failure. Clin Chim Acta 2015;443:78–84.
13. 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.
14. Chin CW, Shah AS, McAllister DA, Cowell SJ, Alam S, Langrish JP, et al. High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis. Eur Heart J 2014;35:2312–21.
15. Cramer G, Bakker J, Gommans F, Brouwer M, Kurvers M, Fouraux M, et al. Relation of highly sensitive cardiac troponin T in hypertrophic cardiomyopathy to left ventricular mass and cardiovascular risk. Am J Cardiol 2014;113:1240–5.
16. Seliger SL, Hong SN, Christenson RH, Kronmal R, Daniels LB, Lima JAC, et al. High-sensitive cardiac troponin T as an early biochemical signature for clinical and subclinical heart failure: MESA (Multi-Ethnic Study of Atherosclerosis). Circulation 2017;135:1494–505.
17. Xanthakis V, Larson MG, Wollert KC, Aragam J, Cheng S, Ho J, et al. Association of novel biomarkers of cardiovascular stress with left ventricular hypertrophy and dysfunction: implications for screening. J Am Heart Assoc 2013;2:e000399.
18. 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.
19. Sou SM, Puelacher C, Twerenbold R, Wagener M, Honegger U, Reichlin T, et al. Direct comparison of cardiac troponin I and cardiac troponin T in the detection of exercise-induced myocardial ischemia. Clin Biochem 2016;49:421–32.
20. Turer AT, Addo TA, Martin JL, Sabatine MS, Lewis GD, Gerszten RE, et al. Myocardial ischemia induced by rapid atrial pacing causes troponin T release detectable by a highly sensitive assay: insights from a coronary sinus sampling study. J Am Coll Cardiol 2011;57: 2398–405.
21. Rosjo H, Kravdal G, Hoiseth AD, Jorgensen M, Badr P, Roysland R, Omland T. Troponin I measured by a high-sensitivity assay in patients with suspected reversible myocardial ischemia: data from the Akershus Cardiac Examination (ACE) 1 study. Clin Chem 2012;58:1565–73.
22. Lee G, Twerenbold R, Tanglay Y, Reichlin T, Honegger U, Wagener M, et al. Clinical benefit of high-sensitivity cardiac troponin I in the detection of exercise-induced myocardial ischemia. Am Heart J 2016;173:8–17.
23. Rademakers F, Engvall J, Edvardsen T, Monaghan M, Sicari R, Nagel E, et al. Determining optimal noninvasive parameters for the prediction of left ventricular remodeling in chronic ischemic patients. Scand Cardiovasc J 2013;47:329–34.
24. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24:987–1003.
25. Queiros S, Barbosa D, Engvall J, Ebbers T, Nagel E, Sarvari SI, et al. Multi-centre validation of an automatic algorithm for fast 4D myocardial segmentation in cine CMR datasets. Eur Heart J Cardiovasc Imaging 2016; 17:1118–27.
26. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. J Cardiovasc Magn Reson 2013; 15:91.
27. Hesse B, Tagil K, Cuocolo A, Anagnostopoulos C, Bardies M, Bax J, et al. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. Eur J Nucl Med Mol Imaging 2005;32:855–97.
28. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Stress myocardial perfusion single-photon emission computed tomography is clinically effective and cost effective in risk stratification of patients with a high likelihood of coronary artery disease (CAD) but no known CAD. J Am Coll Cardiol 2004;43:200–8.
29. Emmett L, Iwanochko RM, Freeman MR, Barolet A, Lee DS, Husain M. Reversible regional wall motion abnormalities on exercise technetium-99m–gated cardiac single photon emission computed tomography predict high-grade angiographic stenoses. J Am Coll Cardiol 2002;39:991–8.
30. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56:254–61.
31. Saenger AK, Beyrau R, Braun S, Cooray R, Dolci A, Freidank H, et al. Multicenter analytical evaluation of a high-sensitivity troponin T assay. Clin Chim Acta 2011; 412:748–54.
32. 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.
33. FDA. 510(k) premarket notification: immunoassay method, troponin subunit. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K162895 (Accessed February, 2017).
34. Peacock W, Baumann BM, Bruton D, Davis TE, Handy B, Jones CW, et al. Efficacy of high-sensitivity troponin T in identifying very-low-risk patients with possible acute coronary syndrome. JAMA Cardiol 2018;3:104–11.
35. Valente MA, Hillege HL, Navis G, Voors AA, Dunselman PH, van Veldhuisen DJ, Damman K. The Chronic Kidney Disease Epidemiology Collaboration equation outperforms the modification of diet in renal disease equation for estimating glomerular filtration rate in chronic systolic heart failure. Eur J Heart Fail 2014;16:86–94.
36. Omland T, White HD. State of the art: blood biomarkers for risk stratification in patients with stable ischemic heart disease. Clin Chem 2017;63:165–76.
37. White HD. Pathobiology of troponin elevations: do elevations occur with myocardial ischemia as well as necrosis? J Am Coll Cardiol 2011;57:2406–8.
38. Korosoglou G, Lehrke S, Mueller D, Hosch W, Kauczor HU, Humpert PM, 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.
39. Kurz K, Giannitsis E, Zehelein J, Katus HA. Highly sensitive cardiac troponin T values remain constant after brief exercise- or pharmacologic-induced reversible myocardial ischemia. Clin Chem 2008;54:1234–8.
40. Seydelmann N, Liu D, Kramer J, Drechsler C, Hu K, Nordbeck P, et al. High-sensitivity troponin: a clinical blood biomarker for staging cardiomyopathy in Fabry disease. J Am Heart Assoc 2016;5:e002839.