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ORIGINAL RESEARCH

Association of High-Sensitivity Troponin T and I Blood Concentrations With All-Cause Mortality and Cardiovascular Outcome in Stable Patients—Results From the INTERCATH Cohort

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BACKGROUND: The association between high-sensitivity troponin T (hsTnT) and high-sensitivity troponin I (hsTnI) and outcome when adjusted for confounders including the angiographical severity of coronary artery disease (CAD) remains largely unknown. We therefore aimed to explore whether hsTnT and hsTnI blood levels increase with CAD severity and add independent predictive information for future major adverse cardiovascular events and all-cause mortality in stable patients.

METHODS AND RESULTS: Patients from the INTERCATH cohort with available coronary angiography and hsTnT and hsTnI concentrations were included. Troponin concentrations were quantified via hsTnT (Roche Elecsys) and hsTnI (Abbott ARCHITECT STAT). To investigate the association of hsTnT and hsTnI with outcome, a multivariable analysis adjusting for classical cardiovascular risk factors, low-density lipoprotein cholesterol, estimated glomerular filtration rate, hs-CRP (high-sensitivity C-reactive protein), NT-proBNP (N-terminal pro–brain natriuretic peptide), and Gensini score was carried out. Of 1829 patients, 27.9% were women, and the mean age was 68.6±10.9 years. Troponin blood concentrations were higher in patients with diagnosed CAD compared with those without. Using a linear regression model current smoking, arterial hypertension, estimated glomerular filtration rate, hs-CRP, NT-proBNP, and CAD severity as graded by the Gensini and SYNTAX scores were associated with high-sensitivity troponin levels. Patients were followed for 4.4 years (25th and 75th percentiles: 4.3, 4.4). After multivariable adjustment, all-cause mortality was predicted by hsTnT (hazard ratio [HR], 1.7 [95% CI, 1.5–2.2], $P<0.001$) as well as hsTnI (HR, 1.5 [95% CI, 1.2–1.8], $P<0.001$). However, only hsTnI (HR, 1.2 [95% CI, 1.0–1.4], $P=0.032$) remained as an independent predictor of major adverse cardiovascular events after adjusting for most possible confounders, including CAD severity (hsTnT: HR, 1.0 [95% CI, 0.9–1.2], $P=0.95$).

CONCLUSIONS: After adjusting for classical cardiovascular risk factors, low-density lipoprotein cholesterol, estimated glomerular filtration rate, hs-CRP, NT-proBNP, and CAD severity, hsTnT and hsTnI were independently associated with all-cause mortality, but only hsTnI was associated with major adverse cardiovascular events in stable patients undergoing coronary angiography.

REGISTRATION: URL: https://clinicaltrials.gov/; Unique identifier: NCT04936438.

Key Words: coronary artery disease ■ Gensini score ■ high-sensitivity troponin ■ outcome prediction ■ SYNTAX score

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CLINICAL PERSPECTIVE

What Is New?

- High-sensitivity troponin I, but not troponin T, was associated with major adverse cardiovascular events after adjusting for confounders, including coronary artery disease severity.

What Are the Clinical Implications?

- High-sensitivity serum troponin contains information across the range of quantifiable concentrations and should be used as a variable for risk prediction.

Nonstandard Abbreviations and Acronyms

hsTnI	high-sensitivity troponin I
hsTnT	high-sensitivity troponin T
MACE	major adverse cardiovascular events

Cardiovascular disease (CVD) remains a leading cause of mortality and morbidity. Patients with coronary artery disease (CAD) are at increased risk for cardiovascular events such as myocardial infarction and stroke.[1] Long-term outcome in patients with CAD is influenced by disease severity with patients exhibiting a more severe form of CAD showing more fatal as well as nonfatal CVD events.[2] Cardiac troponins are an integral part of the contractile apparatus of the myocardium, forming a complex (consisting of troponin T, troponin I, and troponin C) regulating actin–myosin interaction and therefore facilitating myocardial contraction.[3] Whilst troponin T is named after its biding to tropomyosin, troponin I is titled "inhibitory" because of its inhibition of the Mg^{2+}–dependent actomyosin ATPase.[4] Because of their cardiac specificity, troponins have become the mainstay in the diagnosis of patients with suspected acute coronary syndromes, but their use and value in patients with chronic coronary syndromes is limited.[5,6]

Because of the availability of high-sensitivity troponin assays, even minor elevations of troponin can be detected.[7] Release of troponins is caused by different mechanisms, such as acute myocardial necrosis in patients presenting with a myocardial infarction and other circumstances leading to acute or chronic myocardial injury.[8] Troponins have been shown to be associated with CAD severity, even in patients with concomitant chronic kidney disease.[9–13] Furthermore, elevated high-sensitivity troponin T (hsTnT) and high-sensitivity troponin I (hsTnI) blood concentrations are associated with adverse cardiovascular outcome in the general population and in patients with CAD.[14–16]

However, to the best of our knowledge, no simultaneous analysis of hsTnT and hsTnI blood levels has been carried out so far in a cohort of patients with rigorously characterized coronary anatomy, and data about the predictive capability of hsTnT and hsTnI in due consideration of CAD severity and further cardiovascular biomarkers remain sparse. In the current study, we aimed to analyze the independent association of hsTnT and hsTnI blood concentrations with cardiovascular outcome and mortality in a contemporary cohort of patients with angiographically characterized CAD.

METHODS

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Cohort Definition and Inclusion and Exclusion Criteria

The INTERCATH cohort is a single-center, observational, all-comers cohort study of patients admitted to the University Heart and Vascular Center of the University Medical Center Hamburg-Eppendorf, Germany, for coronary angiography. Overall, 3012 patients were recruited from 2015 to 2020. An institutional review committee (local ethics committee [PV4303, Hamburg, Germany]) approved the study, and all patients provided written and informed consent. The study design and rationale are available at ClinicalTrials.gov (NCT04936438) and have previously been described in detail.[17,18] Briefly, patients admitted for coronary angiography were screened for inclusion. Mandatory requirements were aged >18 years, ability to give written informed consent, and sufficient knowledge of the German language. In cases of life-threatening arrhythmias, cardiogenic shock, and further states of hemodynamic instability, patients were not evaluated for inclusion. Standard blood values, medication, and previous history as well as lifestyle parameters were obtained using medical records and a standardized questionnaire; hsTnT and hsTnI were measured in the first 2208 consecutive patients. Subsequently, we excluded 197 patients with acute coronary syndromes, 76 patients after cardiac transplantation, 10 patients with missing estimated glomerular filtration rate (eGFR), and 102 patients without any high-sensitivity troponin values (duplicate missing count possible).

Assessment of CAD Severity and Classical Cardiovascular Risk Factors

The obtained coronary angiograms were graded by experienced interventional cardiologists blinded to hsTnT

and hsTnI concentrations. Severity of CAD was graded using 3 different scoring methods. CAD classification was defined as 1-, 2-, or 3-vessel disease according to the number of affected major epicardial vessels having ≥50% diameter stenosis. Coronary sclerosis was classified as stenosis of <50% vessel lumen in major epicardial vessels. The residual SYNTAX score was calculated using the online available calculator.[19] Gensini segments were defined and scored as published.[20] Classical cardiovascular risk factors were defined as follows: age, male sex, diabetes (self-reported/documented diabetes, self-reported intake of antidiabetics, or an hemoglobin A1c >6.5%), hyperlipoproteinemia (self-reported/documented dyslipidemia or self-reported intake of lipid-lowering medications), current smoking, body mass index, and arterial hypertension (self-reported/documented hypertension or self-reported intake of antihypertensive drugs). Diagnoses were based on patient charts, whereas smoking status was assessed by a standardized questionnaire.

Laboratory Methods

Blood samples were drawn before coronary angiography. Low-density lipoprotein cholesterol (LDL-C), hs-CRP (high-sensitivity C-reactive protein), NT-proBNP (N-terminal pro–brain natriuretic peptide), and eGFR as well as hsTnT (Roche Diagnostics Elecsys) were determined using standard laboratory measures within clinical routine. Previously, a limit of detection of 5 ng/L and a 10% coefficient of variation at 13 ng/L was reported for the used hsTnT assay.[21] The hsTnI concentrations were measured from stored samples at our biomarker laboratory using a commercially available immunoassay (Abbott Diagnostics, ARCHITECT STAT). The limit of detection of the hsTnI assay was 1.9 ng/L, and the intra- and interassay coefficients of variation were reported at 4.51% and 1.47% to 4.46%.

Outcome Ascertainment

Follow-up was carried out by telephone and mail interviews using a standardized questionnaire. In addition, all-cause mortality was determined from the death registry. Outcome parameters were major adverse cardiovascular events (MACE) and all-cause mortality. MACE was defined as cardiovascular death, unplanned revascularization procedure (percutaneous coronary interventions, coronary artery bypass graft surgery), fatal as well as nonfatal myocardial infarction, and stroke. All incident end points were validated by physicians using medical records.

Statistical Analysis

Categorical variables are shown as absolute numbers and percentages. Continuous variables are described by mean±SD or median and 25th percentile and 75th percentile. To describe CAD severity, the population was divided into the following subgroups: by CAD classification (no CAD; coronary sclerosis; 1-, 2-, or 3-vessel disease), by SYNTAX score (no CAD, 0–≤22, >22–<33, ≥33 points), and by Gensini score (no CAD, 0–≤24, >24–≤53, >53 points). The Kruskal–Wallis test was used for between-group comparisons.

The associations of hsTnT and hsTnI with classical cardiovascular risk factors as well as biomarkers LDL-C, eGFR, hs-CRP, and NT-proBNP and the Gensini and SYNTAX scores were evaluated using univariable linear regression. β per SD was calculated if the independent variable was continuous.

The median follow-up time was estimated by the Kaplan–Meier potential follow-up estimator.[18] We designed Kaplan–Meier curves for all-cause mortality and MACE. Survival curve differences were compared using the log-rank test. Cox regression analysis was performed after 48 months of follow-up to investigate the independent association of high-sensitivity troponin with the previously named outcomes unadjusted and adjusting for the following risk factors: age, sex, diabetes, current smoking, body mass index, arterial hypertension, LDL-C, eGFR, hs-CRP, NT-proBNP, and CAD severity (Gensini and SYNTAX scores). With regard to outcome analysis, solely patients with all available covariables needed for the fully adjusted analysis were included in the unadjusted model. Information about the availability of covariables is provided in Table S5.

The proportional hazards assumption was assessed using the methods of Grambsch and Therneau.[22] We found no significant differences in unadjusted and adjusted analyses globally or for the single covariables up to 48 months of follow-up. Therefore, we can assume the proportional hazards (Table S4).

A 2-sided *P*-value of <0.05 was considered statistically significant. All statistical analyses were carried out using R statistical software, version 4.0.3 (R Foundation for Statistical Computing).

RESULTS

Baseline Characteristics

A total of 1829 patients with complete angiographic characterization of CAD were eligible for the current analyses. Mean age was 68.6±10.9 years (27.9% women). Detailed information about classical risk factors and biomarkers at baseline are provided in Table 1 (baseline characteristics for the subgroup with prevalent CAD are shown in Table S1). Overall, more than half of all patients (54.5%) had a history of CAD, and after invasive coronary angiography, 80.8% of participants were diagnosed with prevalent CAD (mean number of diseased vessels, 1.9±1.3; SYNTAX score, 8.0±10.0;

Table 1. Baseline Characteristics (N=1829)

Cardiovascular risk factors	
Age, y	68.6±10.9
Female sex	510 (27.9)
Body mass index, kg/m^2	26.7 (24.1, 30.4)
Arterial hypertension	1455 (81.0)
Hyperlipoproteinemia	1224 (69.9)
Diabetes	379 (20.9)
Current smoking	278 (15.2)
History of smoking	875 (47.8)
Biomarker	
LDL-C, mg/dL	88.0 (66.0, 115.6)
eGFR, mL/min per 1.73 m^2	72.9 (54.6, 87.3)
hs-CRP, mg/dL	0.3 (0.2, 0.9)
NT-proBNP, ng/L	541.0 (175.0, 2000.0)
Severity of CAD	
History of CAD	996 (54.5)
Angiographically diagnosed CAD	1478 (80.8)
No. of affected vessels	1.9±1.3
SYNTAX score	8.0±10.0
Gensini score	20.9±30.2
Troponin blood concentrations	
hsTnT, ng/L	16.0 (9.0, 32.0)
hsTnI, ng/L	8.4 (3.7, 20.9)

Patient characteristics of the total study population. Categorical variables are shown as absolute number (percentage). Continuous variables are described by mean±SD or median (25th percentile, 75th percentile). CAD indicates coronary artery disease; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; hsTnI, high-sensitivity troponin I; hsTnT, high-sensitivity troponin T; LDL-C, low-density lipoprotein cholesterol; and NT-proBNP, N-terminal pro–brain natriuretic peptide.

Gensini score, 20.9±30.2). At baseline, median hsTnT and hsTnI blood concentrations were 16.0 ng/L (9.0 ng/L, 32.0 ng/L) and 8.4 ng/L (3.7 ng/L, 20.9 ng/L) for hsTnT and hsTnI, respectively. The hsTnT and hsTnI blood concentrations were higher in patients with diagnosed CAD compared with those without CAD regardless of the scoring system used (Figure 1). Median troponin blood concentrations according to the CAD severity are provided in Table S2.

Association of hsTnT and hsTnI With Cardiovascular Risk Factors and Biomarkers

Linear regression analysis for the association of hsTnT and hsTnI with classical cardiovascular risk factors as well as LDL-C, eGFR, NT-proBNP, hs-CRP, and SYNTAX and Gensini scores are shown in Table 2. We found a strong association of hsTnT (β, 20.9 [95% CI, 1.9–39.8]) and hsTnI (β, 56.5 [95% CI, 22.1–91.0]) with current smoking status, whereas arterial hypertension was only associated with hsTnT (β, −20.2 [95% CI, −37.8 to −2.6]), but not hsTnI. All other classical cardiovascular risk factors did not show statistically significant associations with hsTnT and hsTnI concentrations (Table 2). Among the investigated biomarkers, hs-CRP was associated with both hsTnT and hsTnI (β per SD, 22.9 [95% CI, 16.0–29.7] and β per SD, 27.2 [95% CI, 14.4–39.9], respectively), whereas eGFR showed a statistically significant association with hsTnI (β per SD, 16.7 [95% CI, 4.2–29.2]). NT-proBNP was associated only with hsTnT (β per SD, 10.3 [95% CI, 3.3–17.2]) and not hsTnI. For the extent of CAD severity, a stable association was found for both troponins. The association with the Gensini score was β per SD 8.0 (95% CI, 0.5–15.5) for hsTnT and 21.9 (95% CI, 8.0–35.9) for hsTnI. The association with the SYNTAX score revealed similar results (Table 2).

Outcome Analyses

Median follow-up time was 4.4 years (4.3 years, 4.4 years). The following MACE occurred during follow-up: 105 cardiovascular deaths, 76 strokes, 71 myocardial infarctions, and 259 unplanned revascularization procedures. All-cause deaths totaled 408 throughout the follow-up period. All-cause mortality as well as MACE increased in the higher quartiles (see Table S3 for further details) of troponin blood concentrations (Figure 2A through 2D). For all-cause mortality, the given quartiles for hsTnT as well as hsTnI showed a stepwise decrease of event-free survival with the lowest event rate in patients within the lowest category of hsTnT and hsTnI blood concentrations and the highest event rate in those within the highest hsTnT and hsTnI quartiles (Figure 2A and 2B). The MACE end point occurred most frequently in patients within the fourth hsTnT quartile (Figure 2C) and those in the third and fourth quartiles of hsTnI (Figure 2D). In both hsTnT and hsTnI, the lowest MACE rate was found in patients in the first quartile (Figure 2C and 2D).

Compared with the first hsTnT and hsTnI quartile, the hazard ratios (HRs) for all-cause mortality showed a stepwise increase for the second quartile (HR, 1.6 [95% CI, 1.3–1.9], P<0.001), third quartile (HR, 1.8 [95% CI, 1.5–2.2], P<0.001), and fourth quartile (HR, 2.4 [95% CI, 2.0–2.9], P<0.001) of hsTnT (hsTnI: HR, 1.4 [95% CI, 1.1–1.7], P<0.001; HR, 1.7 [95% CI, 1.4–2.0], P<0.001; and HR, 1.9 [95% CI, 1.6–2.2], P<0.001) in the unadjusted analysis (Table 3). These associations remained statistically significant even after multivariable adjustment for classical cardiovascular risk factors, eGFR, hs-CRP, NT-proBNP, and CAD severity (Table 3). The highest hazard for MACE during the 48 months of follow-up was found in patients in the third and fourth quartiles of hsTnT (HR, 1.2 [95% CI, 1.0–1.4], P=0.023 for both) and the third quartile of hsTnI (HR, 1.4 [95% CI, 1.2–1.6], P<0.001) compared with the lowest quartile (Table 3). After adjustment for classical cardiovascular risk factors, LDL-C, eGFR, hs-CRP, NT-proBNP, and CAD

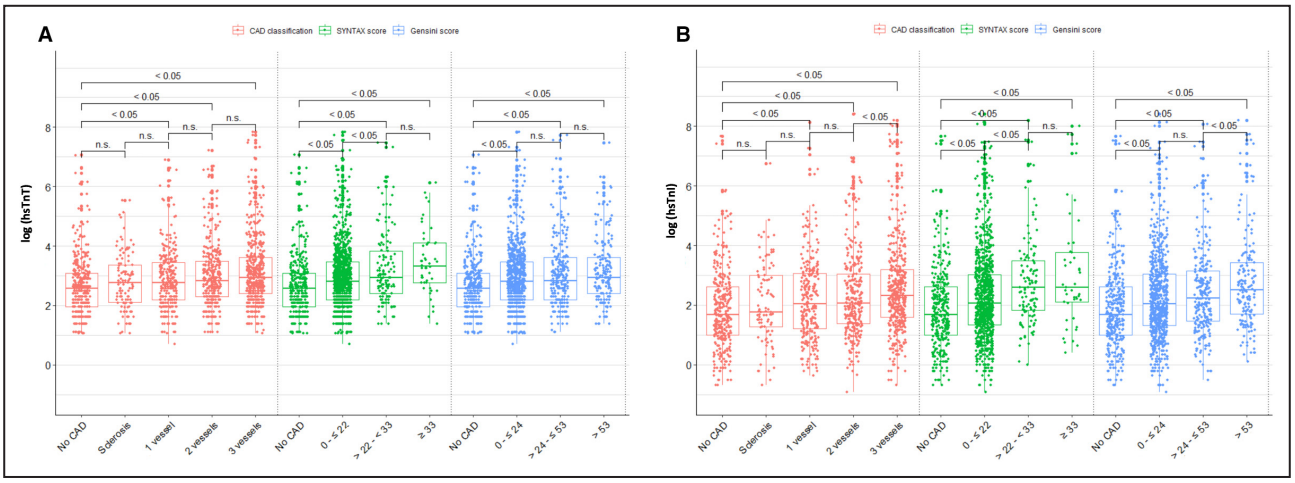

Figure 1. Distribution of logarithmic troponin blood concentrations according to the angiographical severity of CAD.
(A) Concentrations of hsTnT, and (**B**) concentrations of hsTnI. CAD severity was graded using the classical CAD scoring system (red: no CAD; sclerosis; 1-vessel, 2-vessel, or 3-vessel disease), SYNTAX score (green: no CAD, 0–≤22, >22–<33, ≥33), and Gensini score (blue: no CAD, 0–≤24, >24–<53, ≥53). The *P* values (*P*<0.05; *P*<0.001) are shown for differences between the applied categories according to the Kruskal–Wallis test. CAD indicates coronary artery disease; hsTnI, high-sensitivity troponin I; hsTnT, high-sensitivity troponin T; and n.s., not significant.

Table 2. Univariable Linear Regression Model for Troponin T and Troponin I Associated Factors

	hsTnT		hsTnI	
	β (95% CI) or β per SD (95% CI)	*P* value	β (95% CI) or β per SD (95% CI)	*P* value
Classical cardiovascular risk factors				
Age, y	−6.5 (−13.3 to 0.9)	0.060	−8.7 (−21.2 to 3.8)	0.17
Male sex	3.8 (−11.3 to 18.9)	0.62	10.8 (−17.3 to 38.8)	0.45
Diabetes	−2.1 (−18.9 to 14.6)	0.80	−2.9 (−34.0 to 28.1)	0.85
Hyperlipoproteinemia	−3.6 (−18.9 to 11.7)	0.64	13.4 (−14.6 to 41.4)	0.35
LDL-C	−3.41 (−10.29 to 3.46)	0.33	−1.64 (−13.91 to 10.64)	0.79
Current smoking	20.9 (1.9 to 39.8)	0.031	56.5 (22.1 to 91.0)	0.0013
Body mass index	−0.1 (−6.9 to 6.7)	0.98	−5.2 (−17.7 to 7.4)	0.42
Arterial hypertension	−20.2 (−37.8 to −2.6)	<0.001	7.55 (−24.7 to 39.8)	0.65
Biomarker				
eGFR	0.6 (−6.2 to 7.4)	0.87	16.7 (4.2 to 29.2)	0.009
hs-CRP	22.9 (16.0 to 29.7)	<0.001	27.2 (14.4 to 39.9)	<0.001
NT-proBNP	10.3 (3.3 to 17.2)	0.0037	10.0 (−2.7 to 22.7)	0.12
CAD severity				
Gensini score	8.0 (0.5 to 15.5)	0.037	21.9 (8.0 to 35.9)	0.0021
SYNTAX score	8.1 (0.5 to 15.7)	0.036	23.7 (9.6 to 37.7)	<0.001

The β coefficient for categorical variables or the β coefficient per SD for continuous variables and their 95% CIs are shown. CAD indicates coronary artery disease; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; hsTnI, high-sensitivity troponin I; hsTnT, high-sensitivity troponin T; LDL-C, low-density lipoprotein cholesterol; and NT-proBNP, N-terminal pro–brain natriuretic peptide.

severity, no association of MACE with baseline hsTnT blood concentrations was found across all quartiles (Table 3). Here, adjustment for CAD severity as well as for classical cardiovascular risk factors led to a loss of the predictive capabilities of hsTnT for the MACE end point (for further details, see Table S12). For hsTnI, the association with MACE remained statistically significant even in the fully adjusted model for patients in the third and fourth quartiles (third quartile HR, 1.2 [95% CI, 1.1–1.5], *P*=0.012; fourth quartile HR, 1.2 [95% CI, 1.0–1.4], *P*=0.032) (Table 3). This finding was mainly driven by the prediction of incident cardiovascular death (second

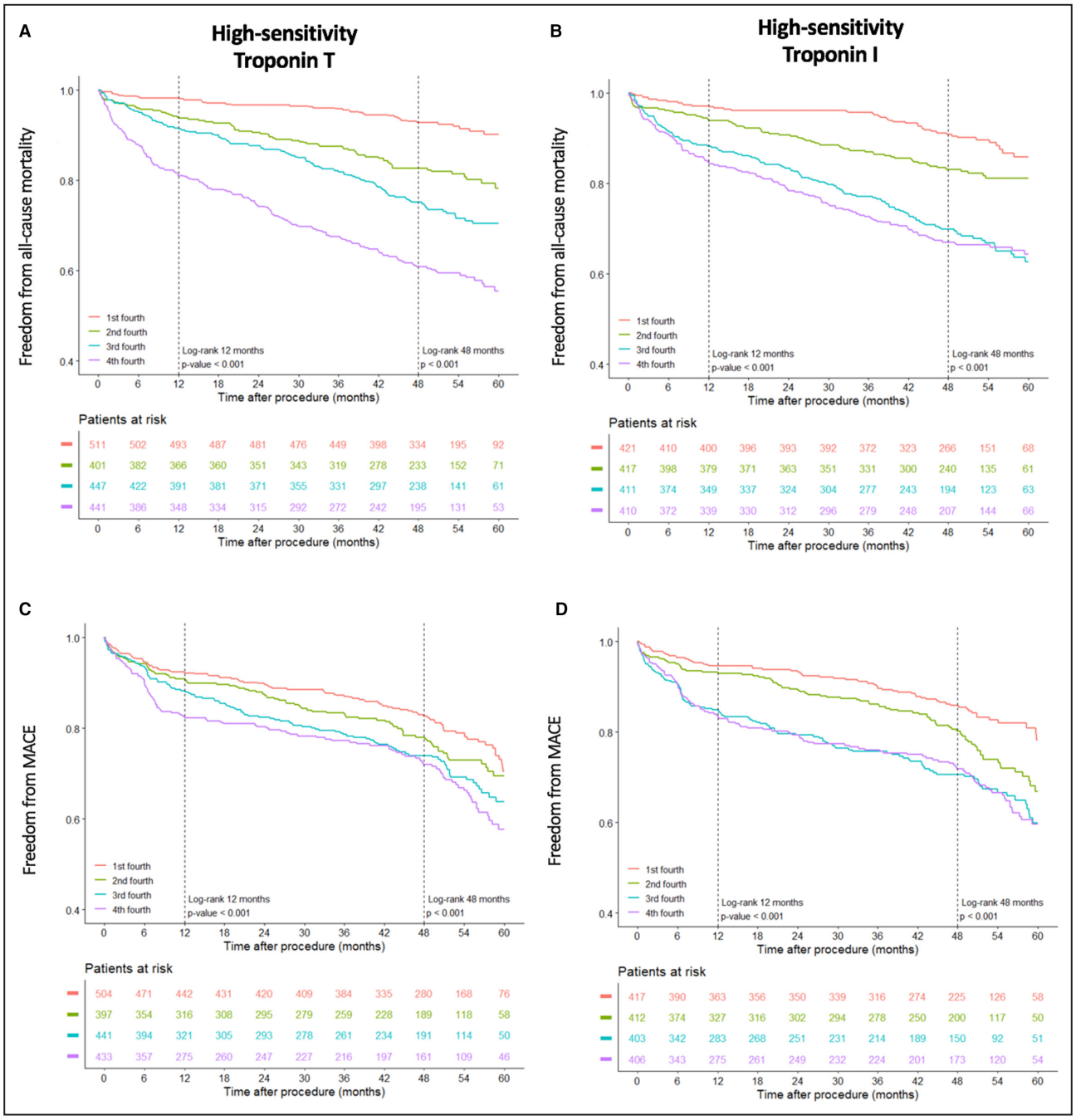

Figure 2. Event-free survival across high-sensitivity troponin T and high-sensitivity troponin I quartiles.
Kaplan–Meier survival curves and the number of patients at risk are shown for (**A** and **B**) all-cause mortality and (**C** and **D**) MACE in the whole study population. MACE was defined as the composite of fatal and nonfatal myocardial infarction, stroke, and need for coronary revascularization. Colored lines represent quartiles of high-sensitivity troponin T and high-sensitivity troponin I. *P* values are given for the log-rank test after 12 and 48 months. MACE indicates major adverse cardiovascular events.

quartile HR, 2.3 [95% CI, 1.2–4.4], *P*=0.016; third quartile HR, 2.9 [95% CI, 1.6–5.3], *P*<0.001; fourth quartile HR, 3.3 [95% CI, 1.8, 6.0], *P*<0.001 for unadjusted analysis); details are provided in Table S6.

Results including Kaplan–Meier curves and multivariable analysis in the subgroup of patients with prevalent CAD are supplied in Table S7 and Figure S1. Furthermore, results after adjustment for hyperlipoproteinemia instead of LDL-C and using the SYNTAX instead of the Gensini score are displayed in Tables S8 and 10 (for the CAD-only population) and S9 and 11 (for the whole population).

Table 3. Association of High-Sensitivity Troponin Quartiles With All-Cause Mortality and Major Adverse Cardiovascular Events

	First vs second quartile	First vs third quartile	First vs fourth quartile
All-cause mortality			
Unadjusted analysis			
hsTnT	1.6 (1.3–1.9), *P*<0.001	1.8 (1.5–2.2), *P*<0.001	2.4 (2.0–2.9), *P*<0.001
hsTnI	1.4 (1.1–1.7), *P*<0.001	1.7 (1.4–2.0), *P*<0.001	1.9 (1.6–2.2), *P*<0.001
Fully adjusted analysis			
hsTnT	1.4 (1.1–1.7), *P*=0.0025	1.5 (1.2–1.8), *P*<0.001	1.7 (1.5–2.2), *P*<0.001
hsTnI	1.2 (1.0–1.5), *P*=0.046	1.3 (1.1–1.6), *P*=0.0017	1.5 (1.2–1.8), *P*<0.001
Major adverse cardiovascular events			
Unadjusted analysis			
hsTnT	1.0 (0.9–1.2), *P*=0.56	1.2 (1.0–1.4), *P*=0.023	1.2 (1.0–1.4), *P*=0.023
hsTnI	1.1 (1.0–1.4), *P*=0.12	1.4 (1.2–1.6), *P*<0.001	1.3 (1.1–1.6), *P*<0.001
Fully adjusted analysis			
hsTnT	0.9 (0.8–1.1), *P*=0.39	1.0 (0.9–1.2), *P*=0.99	1.0 (0.9–1.2), *P*=0.95
hsTnI	1.1 (0.9–1.3), *P*=0.34	1.2 (1.1–1.5), *P*=0.012	1.2 (1.0–1.4), *P*=0.032

Hazard ratios (HRs) and their 95% CIs are shown for unadjusted and fully adjusted analyses after 48 months of follow-up. Adjustment was made for age, sex, diabetes, low-density lipoprotein cholesterol, current smoking, body mass index, arterial hypertension, estimated glomerular filtration rate, high-sensitivity C-reactive protein, N-terminal pro–brain natriuretic peptide, and the Gensini score. hsTnI indicates high-sensitivity troponin I; and hsTnT, high-sensitivity troponin T.

DISCUSSION

This analysis of a large, prospective cohort of clinically stable patients undergoing coronary angiography yielded the following main findings:

1. hsTnT and hsTnI blood concentrations increase with increasing severity of CAD determined by angiography.
2. hsTnT and hsTnI concentrations are predictive of mortality.
3. Only hsTnI blood levels independently predicted MACE after adjustment for classical risk factors, cardiovascular biomarkers, and CAD severity.

These findings suggest that elevated troponin concentrations, in particular hsTnI, could be used to estimate future cardiovascular risk and potentially help selecting patients at highest risk for cardiovascular events, tailoring treatment options for these patients.

In a linear regression analysis, with the exception of smoking status, we found none of the classical cardiovascular risk factors, that is, age, sex, body mass index, diabetes, arterial hypertension, and LDL-C, to be associated with hsTnI blood levels. Interestingly, arterial hypertension was associated with decreased levels of hsTnT, although previous studies have shown increased high-sensitivity troponin levels in patients with hypertension both with and without metabolic syndrome.[23,24] The current findings could be explained by a favorable hemodynamic milieu obtained through adequate antihypertensive medication leading to lower hsTnT levels as was previously observed in patients undergoing treatment with angiotensin-converting enzyme inhibitors or sacubitril/valsartan.[25] For CAD severity as well as eGFR and further cardiovascular biomarkers (ie, hs-CRP and NT-proBNP), we revealed an association with troponin blood concentrations. High-sensitivity troponins have been shown to associate with CAD severity both in studies using invasive coronary angiography as well as computed tomography, potentially as a result of chronic malperfusion as well as microembolisms causing subclinical myocardial ischemia.[9–12,26] Our analysis showed increased concentrations of hsTnI and hsTnT to be associated with more severe CAD. Interestingly, the median hsTnT concentration was slightly above the assay-specific 99th percentile, whereas the median hsTnI blood concentration was found to be below the assay-specific 99th percentile in the majority of patients across all categories of CAD severity.[27,28] Furthermore, we found NT-proBNP to be associated with hsTnT, but not hsTnI. This is contrary to the observations of Nikorowitsch and colleagues in which NT-proBNP correlated with hsTnI and outperformed both hsTnI and hs-CRP in outcome predictions.[29] However, in our study we excluded patients with acute coronary syndromes, which was not the case in the work by Nikorowitsch et al, hence representing a more stable patient clientele, potentially explaining the differing reported results. The prognostic capability of NT-proBNP has been demonstrated in the general population and also in patients with atherosclerotic disease.[29,30] Also, renal function expressed by the eGFR showed a significant association with hsTnI, but not hsTnT. In patients with chronic kidney disease, an adverse cardiovascular outcome has been described as the leading cause of death.[31] The association of hs-CRP with both hsTnT and hsTnI is unsurprising given the crosslink between inflammation, atherosclerosis, and cardiovascular outcome and has previously been demonstrated.[32]

The global association of hsTnT and hsTnI with all-cause mortality has been described previously both in the general population and in patients with stable CAD.[10–12,14,33,34] Next to cardiospecific troponin release caused by myocardial ischemia, it has been hypothesized that elevated troponin concentrations could be a surrogate marker in patients with critical illness,

reflecting an advanced disease state.[35,36] In our study of stable patients undergoing invasive coronary angiography, we confirmed a high all-cause mortality rate in patients in the highest categories of hsTnT and hsTnI. Using classical cardiovascular risk factors and biomarkers in multivariable models, we not only confirmed this association of hsTnT and hsTnI with all-cause mortality but also demonstrated their independent association even after taking the extent of CAD severity into account. For hsTnI, the hazard for all-cause mortality was in the same range as revealed by Tahhan and colleagues after multivariable adjustment.[11] To the best of our knowledge, this independent association of hsTnT and hsTnI with all-cause mortality adjusting for classical cardiovascular risk factors, eGFR, hs-CRP, NT-proBN,P and the Gensini score has not been demonstrated previously.

Recent studies have suggested that hsTnT and hsTnI concentrations are also associated with MACE, such as cardiovascular death, fatal as well as nonfatal myocardial infarction and stroke, and coronary revascularization procedures in patients with chronic coronary syndromes.[10,12,15,16,37] This was also the case in our study, where higher concentrations of hsTnT as well as hsTnI were associated with an increased incidence of MACE during follow-up. Remarkably, after adjustment for classical cardiovascular risk factors, LDL-C, eGFR, hs-CRP, NT-proBNP, and CAD severity as measured by the Gensini score, hsTnI, but not hsTnT, remained independently associated with MACE. This finding could be explained by the supposed superiority of hsTnI as a more specific marker of CVD.[38–40] Two community-based studies, primarily in patients without prevalent CVD, the Atherosclerosis Risk in Communities study and the Generation Scotland Scottish Family Health Study, showed a different association of hsTnT and hsTnI with cardiovascular outcome. In their analyses, hsTnI was a strong predictor of MACE, which also included heart failure, whereas hsTnT was not.[40,41] A noncardiac expression, a racial component, and specific genetic determinants were all discussed with regard to the documented differences in outcome prediction by the 2 troponin subtypes.[38–41] Transferability of these findings to our cohort is limited because both the Atherosclerosis Risk in Communities study and the Generation Scotland Scottish Family Health Study mainly investigated patients without prevalent CVD.

However, other studies also demonstrated hsTnT concentrations to be associated with MACE after adjusting for the number of coronary lesions ≥50% diameter stenosis, representing a simplified CAD classification.[33,42] It can be assumed that the simplified CAD classification, grading severity from 1- to 3-vessel CAD, applied in the aforementioned studies may have led to an underestimation of the overall burden of atherosclerotic disease compared with the Gensini algorithm as used in our study.[33,42] Because the Gensini scoring system itself has been shown to predict outcome, it may be the more appropriate confounder to adjust for.[2]

Our results suggest that serum troponin contains information across the range of quantifiable concentrations, which supports the integration of troponins into risk estimation algorithms as a continuous parameter as has been proposed for acute coronary syndromes.[43] Because of their prognostic relevance, incorporation of hsTnT and hsTnI measurements with clinical risk scores may facilitate the optimization and individualization of treatment intensity in patients. One study showed that the addition of hsTnI into a derived CVD risk score led to the reclassification of 11.9% of patients into the appropriate risk group with regard to cholesterol treatment targets, therefore leading to an improved treatment strategy.[44] Similar findings have been reported for hsTnT.[45] In addition, patients with elevated biomarker concentrations such as troponin exhibited the largest effect of the medical treatment in cardiovascular secondary prevention.[46,47] Our findings substantiate the need for further prospective investigations with regard to the validity of hsTnT and hsTnI in the prediction of cardiovascular outcome and potential troponin-guided treatment algorithms.

Limitations

Strengths of the present study are the precise grading of CAD severity in a contemporary and well-characterized all-comers cohort of patients undergoing coronary angiography. Nevertheless, some limitations merit consideration. First, because the INTERCATH cohort exclusively included patients undergoing coronary angiography, this cohort represents a patient collective with a high pretest probability for CAD. Therefore, findings may not be translated to other patient collectives. Second, hsTnT and hsTnI measurements were only performed at time of inclusion, therefore not displaying potential fluctuation of blood concentrations over time. However, because of the precise clinical characterization of the INTERCATH cohort, only stable patients were included, whereas possible clinical scenarios that may have led to a troponin rise or fall were excluded from current analyses. Third, whether the gradual increase in troponin concentrations is directly attributed to myocardial hypoperfusion or related to the presence of comorbidities such as heart failure or impaired renal function cannot be determined directly in this study. Fourth, with regard to the causes of cardiovascular and noncardiovascular deaths, the direct causes of noncardiovascular deaths are not available in our database. However, all cardiovascular end points (including the individual MACE end points: cardiovascular death, unplanned revascularization [percutaneous coronary

interventions, coronary artery bypass graft surgery], fatal/nonfatal myocardial infarction, or stroke) were validated by physicians using patient charts. Last, despite the precise adjustment for potential confounders, further studies will be needed to investigate the clinical applicability of the reported associations to improve patient outcomes.

CONCLUSIONS

After adjustment for classical cardiovascular risk factors, LDL-C, eGFR, hs-CRP, NT-proBNP, and CAD severity, both hsTnT and hsTnI blood concentrations were associated with all-cause mortality, whereas only elevated hsTnI levels were predictive for MACE. Our data call for a full use of troponin concentrations, in particular hsTnI, as a continuous parameter in risk prediction and merit further investigations of an individualized treatment strategy.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S12
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics.

	All (N=1,478)
Cardiovascular risk factors	
Age (years)	69.9 (10.3)
Female sex (%)	363 (24.6)
Body mass index (kg/m2)	26.8 (24.2, 30.4)
Arterial hypertension (%)	1,233 (84.9)
Hyperlipoproteinemia (%)	1,098 (76.9)
Diabetes mellitus (%)	337 (22.9)
Current smoking (%)	229 (15.5)
History of smoking (%)	738 (49.9)
Biomarker	
LDL-c (mg/dl)	86.0 (65.0, 113.0)
eGFR (ml/min/1.73 m2)	70.8 (52.8, 86.1)
hs-CRP (mg/dL)	0.3 (0.1, 0.9)
NT-proBNP (ng/L)	566.0 (184.0, 2,169.2)
Severity of CAD	
History of CAD (%)	990 (67.0)
No. of affected vessels	2.4 (0.9)
SYNTAX score	10.2 (10.2)
Gensini score	26.7 (31.7)
Troponin blood concentrations	
hsTnT (ng/L)	17.0 (10.0, 34.0)
hsTnI (ng/L)	9.3 (4.2, 23.0)

Patient characteristics of the Coronary artery disease only population. Categorical variables are shown as absolute numbers and percentages. Continuous variables are described by mean ± standard deviation (SD) or median and the 25th percentile and 75th percentile. LDL-c = low density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; CAD = coronary artery disease; PCI = percutaneous coronary intervention; hsTnT = high-sensitivity Troponin T; hsTnI = high-sensitivity Troponin I.

Table S2. Troponin blood levels according to CAD severity categories.

CAD classification						
	No CAD (N=351)	**Coronary sclerosis** (N=110)	**1-vessel disease** (N=297)	**2-vessels disease** (N=349)	**3-vessels disease** (N=665)	***p*-value**
hsTnT, ng/L	13.0 (7.0, 22.0)	16.0 (8.0, 29.1)	16.0 (9.0, 32.0)	17.0 (10.0, 34.3)	19.0 (11.0, 37.1)	<0.001
hsTnI, ng/L	5.3 (2.6, 13.4)	5.8 (3.3, 20.0)	8.1 (3.3, 21.5)	7.9 (4.0, 21.0)	10.9 (5.2, 24.4)	<0.001
SYNTAX score						
	No CAD (N=351)	**0 - ≤22** (N=1063)	**>22 - <33** (N=132)	**≥33** (N=48)		***p*-value**
hsTnT, ng/L	13.0 (7.0, 22.0)	16.0 (9.0, 31.0)	19.0 (11.0, 45.2)	27.5 (16.0, 60.6)		<0.001
hsTnI, ng/L	5.3 (2.6, 13.4)	7.8 (3.7, 20.6)	13.4 (6.2, 32.8)	13.3 (8.1, 43.5)		<0.001
Gensini score						
	No CAD (N=351)	**0 - ≤24** (N=801)	**>24 - ≤53** (N=276)	**>53** (N=181)		***p*-value**
hsTnT, ng/L	13.0 (7.0, 22.0)	16.0 (9.0, 31.0)	17.0 (9.0, 37.1)	19.0 (11.0, 37.1)		<0.001
hsTnI, ng/L	5.3 (2.6, 13.4)	7.3 (3.6, 20.7)	9.4 (4.3, 23.3)	12.1 (5.4, 30.4)		<0.001

Median and the 25th percentile and 75th percentile of troponin blood concentrations (hsTnT/I) according to the CAD classification, SYNTAX score, and Gensini score categories, respectively. The *p*-values are given for differences between the applied categories according to the Kruskal Wallis test. CAD = coronary artery disease; hsTnT = high-sensitivity Troponin T; hsTnI = high-sensitivity Troponin I.

Table S3. Quartiles of high-sensitivity Troponin (hsTn) utilized for Outcome analyses.

	1st Quartile (n=478)	**2nd Quartile** (n=433)	**3rd Quartile** (n=467)	**4th Quartile** (n=436)
hsTnT (ng/L)	2.0, 9.0	9.0, 16.0	16.0, 32.0	32.0, 2540.0
	1st Quartile (n=419)	**2nd Quartile** (n=417)	**3rd Quartile** (n=418)	**4th Quartile** (n=418)
hsTnI (ng/L)	0.2, 3.7	3.7, 8.4	8.4, 20.9	20.9, 4526.5

hsTnT = high-sensitivity Troponin T; hsTnI = high-sensitivity Troponin I.

Table S4. Assessment of the proportional hazards assumption for all-cause mortality and Major adverse cardiovascular events in the whole study population.

	All-cause mortality		Major adverse cardiovascular events	
	Two sided p-values of a score test for addition of the time-dependent term			
	hsTnT	hsTnI	hsTnT	hsTnI
Unadjusted Analysis	0.08 (Global)	0.21 (Global)	0.52 (Global)	0.05 (Global)
Fully Adjusted Analysis including Gensini Score	0.50 (Global)	0.51 (Global)	0.71 (Global)	0.34 (Global)
Troponin	0.24	0.38	0.79	0.11
age	0.28	0.28	0.12	0.05
sex	0.32	0.32	0.71	0.61
diabetes	0.52	0.47	0.44	0.63
LDL-c	0.60	0.49	0.29	0.44
Current smoking	0.75	0.68	0.81	0.71
body mass index	0.36	0.19	0.10	0.32
hypertension	0.42	0.41	0.45	0.70
eGFR	0.75	0.71	0.91	0.91
hs-CRP	0.83	0.70	0.21	0.25
NT-proBNP	0.42	0.42	0.72	0.79
Gensini score	0.11	0.11	0.74	0.82

Adjustment was made for age, sex, diabetes mellitus, LDL-c, current smoking, body mass index, arterial hypertension, eGFR, hs-CRP, NT-proBNP, and the Gensini score. HsTnT = high-sensitivity Troponin T; hsTnI = high-sensitivity Troponin I; LDL-c = low density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Table S5. **Availability of variables for high-sensitivity Troponin T and I according to Troponin Quartiles**.

High-sensitivity Troponin T					High-sensitivity Troponin I				
	1st Quartile (N=514)	**2nd Quartile (N=403)**	**3rd Quartile (N=450)**	**4th Quartile (N=447)**		**1st Quartile (N=514)**	**2nd Quartile (N=403)**	**3rd Quartile (N=450)**	**4th Quartile (N=447)**
Age (%)	514 (100)	403 (100)	450 (100)	447 (100)	Age (%)	514 (100)	403 (100)	450 (100)	447 (100)
Male (%)	514 (100)	403 (100)	450 (100)	447 (100)	Male (%)	514 (100)	403 (100)	450 (100)	447 (100)
Diabetes (%)	513 (99.8)	400 (99.3)	448 (99.6)	445 (99.6)	Diabetes (%)	513 (99.8)	400 (99.3)	448 (99.6)	445 (99.6)
Current Smoking (%)	514 (100)	403 (100)	450 (100)	447 (100)	Current Smoking (%)	514 (100)	403 (100)	450 (100)	447 (100)
Body mass index (%)	512 (99.6)	402 (99.8)	448 (99.6)	447 (100)	Body mass index (%)	512 (99.6)	402 (99.8)	448 (99.6)	447 (100)
Arterial Hypertension (%)	505 (98.2)	399 (99.0)	437 (97.1)	440 (98.4)	Arterial Hypertension (%)	505 (98.2)	399 (99.0)	437 (97.1)	440 (98.4)
eGFR (%)	514 (100)	403 (100)	450 (100)	447 (100)	eGFR (%)	514 (100)	403 (100)	450 (100)	447 (100)
hs-CRP (%)	497 (96.7)	392 (97.3)	427 (94.9)	412 (92.2)	hs-CRP (%)	497 (96.7)	392 (97.3)	427 (94.9)	412 (92.2)
NT-proBNP (%)	502 (97.7)	397 (98.5)	430 (95.6)	423 (94.6)	NT-proBNP (%)	502 (97.7)	397 (98.5)	430 (95.6)	423 (94.6)
LDL-c (%)	498 (96.9)	390 (96.8)	432 (96.0)	431 (96.4)	LDL-c (%)	498 (96.9)	390 (96.8)	432 (96.0)	431 (96.4)
Gensini score (%)	463 (90.1)	360 (89.3)	390 (86.7)	381 (85.2)	Gensini score (%)	463 (90.1)	360 (89.3)	390 (86.7)	381 (85.2)
SYNTAX score (%)	458 (89.1)	357 (88.6)	389 (86.4)	375 (83.9)	SYNTAX score (%)	458 (89.1)	357 (88.6)	389 (86.4)	375 (83.9)

LDL-c = low density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Table S6. Association of high-sensitivity Troponin quartiles with MACE, cardiovascular deaths, myocardial infarction, stroke, and revascularization procedures.

Major adverse cardiovascular events			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.9-1.2), p=0.56	1.2 (1.0-1.4), p=0.023	1.2 (1.0-1.4), p=0.023
hsTnI, HR (95% CI)	1.1 (1.0-1.4), p=0.12	1.4 (1.2-1.6), p<0.001	1.3 (1.1-1.6), p<0.001
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	0.9 (0.8-1.1), p=0.39	1.0 (0.9-1.2), p=0.99	1.0 (0.9-1.2), p=0.95
hsTnI, HR (95% CI)	1.1 (0.9-1.3), p=0.34	1.2 (1.1-1.5), p=0.012	1.2 (1.0-1.4), p=0.032
Cardiovascular death			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.4 (0.9, 2.1), p=0.094	1.6 (1.1, 2.3), p=0.023	2.3 (1.6, 3.2), p<0.001
hsTnI, HR (95% CI)	2.3 (1.2, 4.4), p=0.016	2.9 (1.6, 5.3), p<0.001	3.3 (1.8, 6.0), p<0.001
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.2 (0.8, 1.8), p=0.42	1.2 (0.8, 1.7), p=0.47	1.6 (1.1, 2.3), p=0.0096
hsTnI, HR (95% CI)	2.0 (1.0, 3.9), p=0.045	2.3 (1.2, 4.3), p=0.008	2.7 (1.5, 4.9), p=0.0014
Myocardial infarction			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**

hsTnT, HR (95% CI)	1.2 (0.8-1.8), p=0.35	1.5 (1.1, 2.2), p=0.021	0.9 (0.6, 1.5), p=0.78
hsTnI, HR (95% CI)	1.1 (0.7, 1.7), p=0.79	1.4 (0.9, 2.1), p=0.11	1.2 (0.8, 1.9), p=0.36
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.2 (0.8, 1.8), p=0.43	1.5 (1.0, 2.2), p=0.056	0.9 (0.5, 1.5), p=0.63
hsTnI, HR (95% CI)	1.0 (0.7, 1.6), p=0.88	1.4 (0.9, 2.2), p=0.12	1.1 (0.7, 1.8), p=0.61
Stroke			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.1 (0.8, 1.5), p=0.48	1.0 (0.7, 1.4), p=0.92	0.9 (0.6, 1.3), p=0.55
hsTnI, HR (95% CI)	1.1 (0.7, 1.5), p=0.76	1.2 (0.8, 1.6), p=0.36	0.9 (0.6, 1.3), p=0.61
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.7, 1.4), p=0.9	0.9 (0.6, 1.3), p=0.51	0.8 (0.5, 1.2), p=0.25
hsTnI, HR (95% CI)	1.0 (0.7, 1.4), p=0.99	1.1 (0.8, 1.6), p=0.6	0.9 (0.6, 1.3), p=0.49
Revascularization procedures			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.9, 1.2), p=0.89	1.0 (0.9, 1.2), p=0.89	1.0 (0.8, 1.2), p=0.87
hsTnI, HR (95% CI)	1.1 (0.9, 1.3), p=0.44	1.2 (1.0, 1.4), p=0.036	1.2 (1.0, 1.4), p=0.054

Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.8, 1.1), p=0.56	1.0 (0.8, 1.1), p=0.6	1.0 (0.8, 1.2), p=0.8
hsTnI, HR (95% CI)	1.1 (0.9-1.3), p=0.42	1.2 (1.0-1.4), p=0.077	1.2 (1.0-1.5), p=0.045

Hazard ratios (HR) and their 95% confidence interval (CI) are given for unadjusted and fully adjusted analyses after 48 months of follow-up. Adjustment was made for age, sex, diabetes mellitus, LDL-c, current smoking, body mass index, arterial hypertension, eGFR, hs-CRP, NT-proBNP, and the Gensini score. hsTnT = high-sensitivity Troponin T; hsTnI = high-sensitivity Troponin I; LDL-c = low density lipoprotein; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; MACE = Major adverse cardiovascular events.

Table S7. Unadjusted and adjusted Cox regression models for the association of high-sensitivity Troponin Quartiles with all-cause mortality and major adverse cardiovascular events after 48 months of follow-up in the in the CAD only population.

All-cause mortality			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.9 (1.5, 2.4), p<0.001	2.1 (1.6, 2.6), p<0.001	2.6 (2.1, 3.3), p<0.001
hsTnI, HR (95% CI)	1.3 (1.1, 1.7), p=0.0066	1.7 (1.4, 2.1), p<0.001	1.9 (1.5, 2.3), p<0.001
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.7 (1.3, 2.1), p<0.001	1.7 (1.3, 2.1), p<0.001	2.0 (1.6, 2.6), p<0.001
hsTnI, HR (95% CI)	1.2 (1.0, 1.5), p=0.12	1.4 (1.1, 1.7), p<0.001	1.5 (1.2, 1.8), p<0.001
Major adverse cardiovascular events			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.9, 1.2), p=0.60	1.1 (1.0, 1.3), p=0.18	1.1 (0.9, 1.3), p=0.21
hsTnI, HR (95% CI)	1.2 (1.0, 1.4), p=0.087	1.3 (1.1, 1.6), p<0.001	1.3 (1.1, 1.5), p=0.0066
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	0.9 (0.8, 1.1), p=0.51	1.0 (0.8, 1.1), p=0.62	1.0 (0.8, 1.2), p=0.76
hsTnI, HR (95% CI)	1.1 (0.9, 1.3), p=0.20	1.3 (1.1, 1.5), p=0.011	1.2 (1.0, 1.4), p=0.043

Hazard ratios (HR) and their 95% confidence interval (CI) are given. Adjustment was made for age, sex, diabetes, hyperlipoproteinemia, current smoking, body mass index, hypertension, LDL-c, eGFR, hs-CRP, NT-proBNP, and the Gensini score. hsTnT = high-sensitivity Troponin T; hsTnI = high-sensitivity Troponin I; LDL-c = low density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Table S8. Unadjusted and adjusted Cox regression models for the association of high-sensitivity Troponin Quartiles with all-cause mortality and major adverse cardiovascular events after 48 months of follow-up in the in the CAD only population.

All-cause mortality			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.9 (1.5, 2.4), p<0.001	2.1 (1.6, 2.6), p<0.001	2.6 (2.1, 3.3), p<0.001
hsTnI, HR (95% CI)	1.3 (1.1, 1.7), p=0.0066	1.7 (1.4, 2.1), p<0.001	1.9 (1.5, 2.3), p<0.001
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.7 (1.3, 2.1), p<0.001	1.7 (1.3, 2.1), p<0.001	2.0 (1.6, 2.6), p<0.001
hsTnI, HR (95% CI)	1.2 (0.9, 1.5), p=0.14	1.4 (1.1, 1.7), p=0.0011	1.5 (1.2, 1.8), p<0.001
Major adverse cardiovascular events			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.9, 1.2), p=0.60	1.1 (1.0, 1.3), p=0.18	1.1 (0.9, 1.3), p=0.21
hsTnI, HR (95% CI)	1.2 (1.0, 1.4), p=0.087	1.3 (1.1, 1.6), p<0.001	1.3 (1.1, 1.5), p=0.0066
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.8, 1.1), p=0.65	1.0 (0.8, 1.1), p=0.59	1.0 (0.8, 1.2), p=0.91
hsTnI, HR (95% CI)	1.1 (0.9, 1.3), p=0.49	1.2 (1.0, 1.5), p=0.014	1.2 (1.0, 1.4), p=0.056

Hazard ratios (HR) and their 95% confidence interval (CI) are given. Adjustment was made for age, sex, diabetes, hyperlipoproteinemia, current smoking, body mass index, hypertension, eGFR, hs-CRP, NT-proBNP, and the Gensini score. hsTnT = high-sensitivity Troponin T; hsTnI = high-sensitivity Troponin I; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Table S9. Unadjusted and adjusted Cox regression models for the association of high-sensitivity Troponin quartiles with all-cause mortality and major adverse cardiovascular events after 48 months of follow-up in the whole study population.

All-cause mortality			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.6 (1.3-1.9), p<0.001	1.8 (1.5-2.2), p<0.001	2.4 (2.0-2.9), p<0.001
hsTnI, HR (95% CI)	1.4 (1.1-1.7), p<0.001	1.7 (1.4-2.0), p<0.001	1.9 (1.6-2.2), p<0.001
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.4 (1.1-1.7), p=0.0013	1.5 (1.2-1.8), p<0.001	1.9 (1.5-2.3), p<0.001
hsTnI, HR (95% CI)	1.2 (1.0-1.4), p=0.11	1.3 (1.1-1.6), p=0.0023	1.5 (1.2-1.8), p<0.001
Major adverse cardiovascular events			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.9-1.2), p=0.56	1.2 (1.0-1.4), p=0.023	1.2 (1.0-1.4), p=0.023
hsTnI, HR (95% CI)	1.1 (1.0-1.4), p=0.12	1.4 (1.2-1.6), p<0.001	1.3 (1.1-1.6), p<0.001
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.8-1.1), p=0.61	1.0 (0.9-1.2), p=0.86	1.0 (0.9-1.2), p=0.80
hsTnI, HR (95% CI)	1.1 (0.9-1.3), p=0.51	1.2 (1.0-1.5), p=0.012	1.2 (1.0-1.4), p=0.028

Hazard ratios (HR) and their 95% confidence interval (CI) are given. Adjustment was made for age, sex, diabetes mellitus, hyperlipoproteinemia, current smoking, body mass index, arterial hypertension, eGFR, hs-CRP, NT-proBNP, and the Gensini score. hsTnT = high-sensitivity Troponin T; hsTnI = high-sensitivity Troponin I; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Table S10. Unadjusted and adjusted Cox regression models for the association of high-sensitivity Troponin Quartiles with all-cause mortality and major adverse cardiovascular events after 48 months of follow-up in the in the CAD only population.

All-cause mortality			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.9 (1.5, 2.4), p<0.001	2.1 (1.6, 2.6), p<0.001	2.6 (2.1, 3.3), p<0.001
hsTnI, HR (95% CI)	1.3 (1.1, 1.7), p=0.0066	1.7 (1.4, 2.1), p<0.001	1.9 (1.5, 2.3), p<0.001
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.7 (1.3, 2.1), p<0.001	1.7 (1.3, 2.1), p<0.001	2.0 (1.6, 2.6), p<0.001
hsTnI, HR (95% CI)	1.2 (1.0, 1.5), p=0.12	1.4 (1.1, 1.7), p=0.0011	1.5 (1.2, 1.8), p<0.001
Major adverse cardiovascular events			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.9, 1.2), p=0.60	1.1 (1.0, 1.3), p=0.18	1.1 (0.9, 1.3), p=0.21
hsTnI, HR (95% CI)	1.2 (1.0, 1.4), p=0.087	1.3 (1.1, 1.6), p<0.001	1.3 (1.1, 1.5), p=0.0066
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.8, 1.1), p=0.67	1.0 (0.8, 1.2), p=0.78	1.0 (0.8, 1.2), p=0.85
hsTnI, HR (95% CI)	1.1 (0.9, 1.3), p=0.29	1.2 (1.0, 1.5), p=0.015	1.2 (1.0, 1.4), p=0.0042

Hazard ratios (HR) and their 95% confidence interval (CI) are given. Adjustment was made for age, sex, diabetes, current smoking, body mass index, hypertension, LDL-c, eGFR, hs-CRP, NT-proBNP, and the SYNTAX score. hsTnT = high-sensitivity Troponin T; hsTnI = high-sensitivity Troponin I; LDL-c = low density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Table S11. Unadjusted and adjusted Cox regression models for the association of high-sensitivity Troponin Quartiles with all-cause mortality and major adverse cardiovascular events after 48 months of follow-up in the whole study population.

All-cause mortality			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.6 (1.3-1.9), p<0.001	1.8 (1.5-2.2), p<0.001	2.4 (2.0-2.9), p<0.001
hsTnI, HR (95% CI)	1.4 (1.1-1.7), p<0.001	1.7 (1.4-2.0), p<0.001	1.9 (1.6-2.2), p<0.001
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.4 (1.1-1.7), p=0.0025	1.5 (1.2-1.8), p<0.001	1.8 (1.5-2.2), p<0.001
hsTnI, HR (95% CI)	1.2 (1.0-1.5), p=0.044	1.3 (1.1-1.6), p=0.0016	1.5 (1.2-1.8), p<0.001
Major adverse cardiovascular events			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.9-1.2), p=0.56	1.2 (1.0-1.4), p=0.023	1.2 (1.0-1.4), p=0.023
hsTnI, HR (95% CI)	1.1 (1.0-1.4), p=0.12	1.4 (1.2-1.6), p<0.001	1.3 (1.1-1.6), p<0.001
Fully Adjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.8-1.1), p=0.55	1.0 (0.9-1.2), p=0.73	1.0 (0.8-1.2), p=0.94
hsTnI, HR (95% CI)	1.1 (0.9-1.3), p=0.44	1.2 (1.0-1.5), p=0.017	1.2 (1.0-1.4), p=0.034

Hazard ratios (HR) and their 95% confidence interval (CI) are given. Adjustment was made for age, sex, diabetes, current smoking, body mass index, hypertension, LDL-c, eGFR, hs-CRP, NT-proBNP, and the SYNTAX score. hsTnT = high-sensitivity Troponin T; hsTnI = high-sensitivity Troponin I; LDL-c = low density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

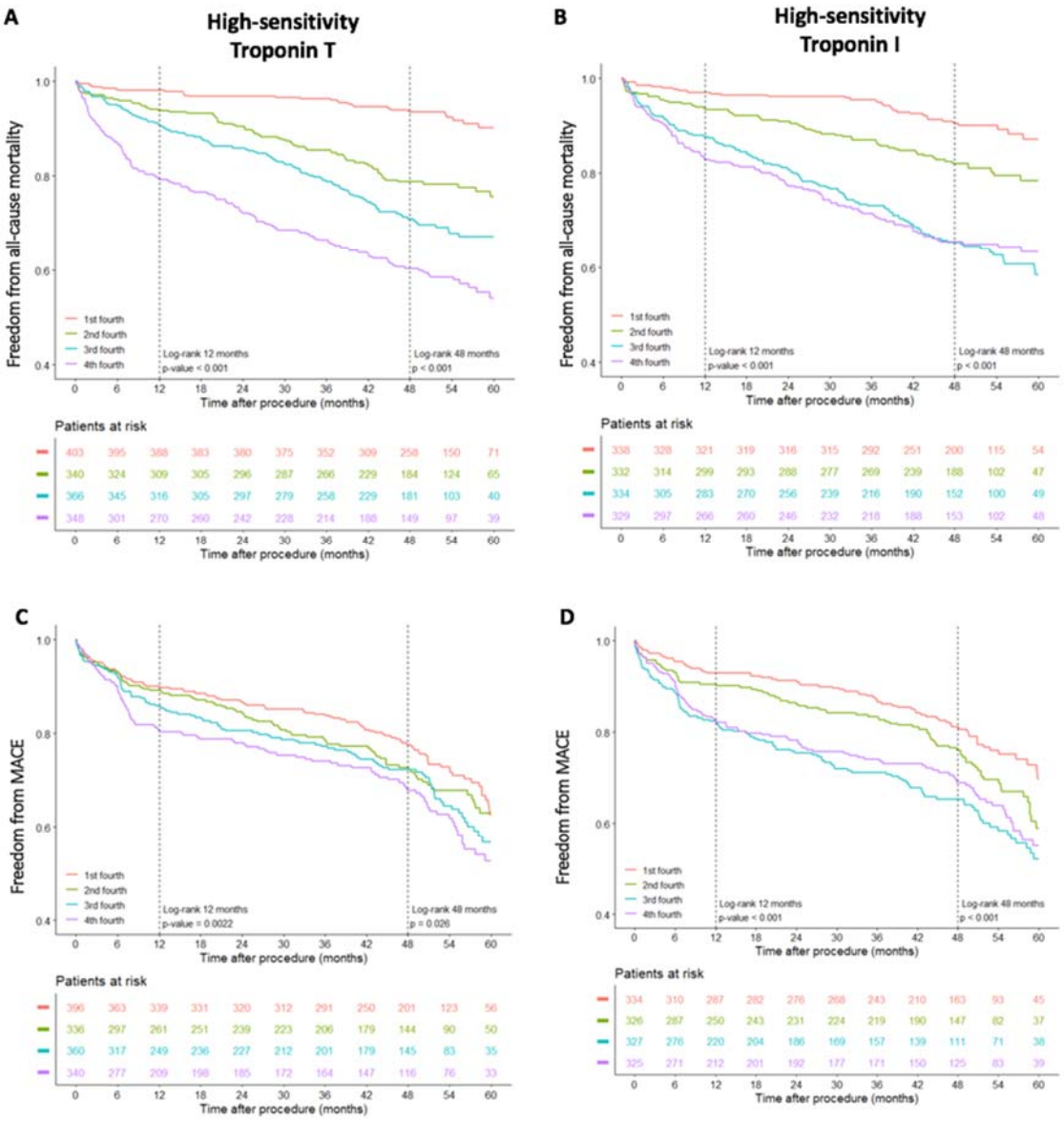
Table S12. Association of high-sensitivity Troponin quartiles with Major adverse cardiovascular events.

Major adverse cardiovascular events			
Unadjusted Analysis	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.9-1.2), p=0.56	1.2 (1.0-1.4), p=0.023	1.2 (1.0-1.4), p=0.023
hsTnI, HR (95% CI)	1.1 (1.0-1.4), p=0.12	1.4 (1.2-1.6), p<0.001	1.3 (1.1-1.6), p<0.001
Adjustment for the Gensini Score	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.9, 1.2), p=0.79	1.2 (1.0, 1.3), p=0.056	1.1 (1.0, 1.3), p=0.075
hsTnI, HR (95% CI)	1.1 (0.9, 1.3), p=0.19	1.3 (1.1, 1.6), p<0.001	1.3 (1.1, 1.5), p=0.0035
Adjustment for CVRF	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.8, 1.1), p=0.74	1.1 (0.9, 1.3), p=0.37	1.1 (0.9, 1.3), p=0.2
hsTnI, HR (95% CI)	1.1 (0.9, 1.3), p=0.35	1.3 (1.1, 1.5), p=0.0029	1.3 (1.1, 1.5), p=0.0093
Adjustment for CVRF + eGFR	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.8, 1.1), p=0.66	1.0 (0.9, 1.2), p=0.56	1.1 (0.9, 1.2), p=0.55
hsTnI, HR (95% CI)	1.1 (0.9, 1.3), p=0.38	1.3 (1.1, 1.5), p=0.0059	1.3 (1.1, 1.5), p=0.0093
Adjustment for CVRF + hs-CRP	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.8, 1.1), p=0.73	1.1 (0.9, 1.2), p=0.42	1.1 (0.9, 1.3), p=0.23

hsTnI, HR (95% CI)	1.1 (0.9, 1.3), p=0.35	1.3 (1.1, 1.5), p=0.003	1.3 (1.1, 1.5), p=0.0045
Adjustment for CVRF + NT-proBNP	**1st vs. 2nd Quartile**	**1st vs. 3rd Quartile**	**1st vs. 4th Quartile**
hsTnT, HR (95% CI)	1.0 (0.8, 1.1), p=0.72	1.1 (0.9, 1.2), p=0.41	1.1 (0.9, 1.2), p=0.28
hsTnI, HR (95% CI)	1.1 (0.9, 1.3), p=0.35	1.3 (1.1, 1.5), p=0.0033	1.3 (1.1, 1.5), p=0.0057

Hazard ratios (HR) and their 95% confidence interval (CI) are given for unadjusted and adjusted analyses after 48 months of follow-up. Adjustment was made for the Gensini Score, CVRF (classical cardiovascular risk factors - age, sex, diabetes mellitus, LDL-c, current smoking, body mass index, arterial hypertension), CVRF + eGFR, CVRF + hs-CRP and CVRF + NT-proBNP. hsTnT = high-sensitivity Troponin T; hsTnI = high-sensitivity Troponin I; LDL-c = low density lipoprotein; eGFR = estimated glomerular filtration rate; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

Figure S1. Event-free survival across hsTnT and hsTnI quartiles.



Kaplan-Meier survival curves and the number of patients at risk are shown all-cause mortality (A and B) and major adverse cardiac events (MACE; C and D) in the Coronary artery disease only population. MACE was defined as the composite of fatal and non-fatal myocardial infarction, stroke and need for coronary revascularization. Coloured lines represent quartiles of hsTnT and hsTnI, respectively. p-values are given for the log-rank test after 12 and 48 months.