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High-sensitivity Troponin T in relation to coronary plaque characteristics in patients with stable coronary artery disease; results of the ATHEROREMO-IVUS study

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ABSTRACT

Background and aims: To assess the relationship between the extent and phenotype of coronary atherosclerosis, as assessed by in-vivo grayscale and radiofrequency intravascular ultrasound (IVUS), and circulating Troponin levels in patients with established stable coronary artery disease (CAD).

Methods: In this single-center, cross-sectional analysis, high-sensitivity Troponin T (hsTnT) was measured and IVUS was performed in a predefined non-stenotic segment of a non-culprit coronary artery in 231 patients with stable CAD undergoing elective angiography.

Results: HsTnT was detectable (>3 pg/mL) in 212 patients (92%) and a concentration above 14 pg/mL was observed in 19.5%. Normalised segmental plaque volumes were positively associated with hsTnT levels (25.0 mm³ increase in segmental plaque volume per SD increase in ln-transformed hsTnT, 95% CI: 6.0–44.0, p = 0.010). Higher hsTnT levels were measured in patients with a virtual histology derived thin-cap fibroatheroma (VH-TCFA, adj. odds ratio for presence of VH-TCFA = 1.52 per SD increase in ln-transformed hsTnT, 95% CI: 1.10–2.11, p = 0.011). Patients with a VH-TCFA had a 2-fold increased prevalence of hsTnT concentration ≥14 pg/mL (adj. OR 2.35, 95% CI: 1.12–4.91, p = 0.024). In addition, a 3-fold increased prevalence of hsTnT concentration ≥14 pg/mL was observed in patients with a VH-TCFA with a lesional plaque volume higher than the median (adj. OR 3.36, 95% CI: 1.44–7.84, p = 0.005).

Conclusions: Segmental plaque volume and presence of VH-TCFA lesions are associated with higher circulating hsTnT concentrations in stable CAD patients. Subclinical plaque rupture or erosion and distal embolisation may be hypothesized as a potential pathophysiological mechanism with respect to Troponin elevation and its relation with adverse outcome in this patient population.

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1. Introduction

Cardiac Troponin is the preferred biochemical marker for diagnostic use in patients with a suspected acute coronary syndrome (ACS) [1]. However Troponin elevation also has prognostic

relevance in patients *without chestpain at rest*. In ambulatory patients with established stable coronary artery disease (CAD) as enrolled in the Heart and Soul study, Troponin T (TnT) was detectable in 6% of the study population when using a conventional TnT assay [2]. With the recent introduction of the high-sensitivity Troponin T assay (hsTnT), circulating TnT levels could be detected in 81% of the same study population of ambulatory patients with stable CAD [3]. In these 984 patients, higher hsTnT levels were, amongst others, associated with greater inducible ischemia, worse treadmill exercise capacity and lower left ventricular ejection

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fraction. Moreover, hsTnT elevation remained independently predictive of cardiovascular mortality, myocardial infarction (MI) and heart failure after adjustment for abnormalities in cardiac structure and function [3]. Similar associations between hsTnT elevation and increased risk for major adverse cardiovascular events (MACE) in ambulatory patients with stable CAD were also observed in post-hoc analyses of the PEACE trial [4], the BARI-2D trial [5] and in a study of stable CAD patients participating in an in-hospital rehabilitation program [6].

Yet, despite these positive associations between hsTnT and long-term outcome, currently no data are available on the association between coronary plaque characteristics and hsTnT elevation in patients with stable CAD. However, the assessment of such a possible relationship is imperative in order to understand the etiology of the Troponin elevation, as well as to gain insight into the mechanisms by which Troponin elevation exerts its adverse impact on prognosis [7]. Hence, our objective was to assess the relationship between coronary plaque characteristics and phenotype, as assessed by in-vivo grayscale and radiofrequency intravascular ultrasound (IVUS), and Troponin levels in patients with established stable CAD.

2. Methods

2.1. Study population

The design, detailed inclusion and exclusion criteria and initial results of the prospective, single-center, observational, European Collaborative Project on Inflammation and Vascular Wall Remodeling in Atherosclerosis – Intravascular Ultrasound (ATHEROREMO-IVUS) study have been described previously [8,9]. The study enrolled 581 patients, but for the current analysis 318 ACS patients were omitted, since hsTnT levels in those patients are obviously more determined by intracoronary thrombosis due to acute plaque rupture of a culprit vessel and subsequent varying degrees of myocardial necrosis, and to a much lesser extent by the vessel characteristics of a non-culprit vessel, as investigated in the ATHEROREMO-IVUS study. All of the patients had stable angina, were ambulatory and presented at the discretion of the referring physician for a planned and elective admission for angiography after consenting at the out-patient clinic. None of the patients were admitted for acute chest pain or dynamic ECG changes at rest. Patients with an indication for angiography other than stable angina pectoris (SAP, $n = 9$) and those with known confounders of Troponin elevation [10] such as history of heart failure ($n = 13$) or renal insufficiency ($n = 19$, nine of whom had concomitant heart failure) were omitted.

The ATHEROREMO-IVUS study was approved by the medical ethics committee of the Erasmus MC. The study was performed in accordance with the criteria described in the declaration of Helsinki. Written informed consent was obtained from all included patients. ATHEROREMO-IVUS is registered in ClinicalTrials.gov, number NCT01789411.

2.2. High-sensitivity Troponin T

Blood samples were drawn from the 6 French arterial sheath prior to catheter insertion. TnT was measured with both a conventional fourth generation assay and a high-sensitivity assay on the Cobas 8000 modular analyzer platform (Roche Diagnostics GmbH, Mannheim, Germany). The diagnostic range of the high-sensitivity assay is 3–10.000 pg/mL with a coefficient of variation of 9% at the 99th percentile value of 14 pg/mL [11]. Laboratory personnel were blinded for baseline patient characteristics and IVUS data.

2.3. Intracoronary ultrasound imaging

Subsequent to the standard angiography and PCI (when applicable), IVUS of a non-culprit coronary artery was performed with the Volcano s5/s5i Imaging System (Volcano Corp., San Diego, CA, USA) [9]. The IVUS target segment of the non-culprit coronary artery was required to be at least 40 mm in length and without significant luminal narrowing (<50% stenosis) as assessed by on-line angiography. Selection of the non-culprit vessel was predefined in the study protocol. The IVUS images were analyzed off-line by an independent core laboratory (Cardialysis BV, Rotterdam, the Netherlands). The core laboratory personnel were blinded for baseline patient characteristics and TnT and hsTnT levels.

Plaque burden was defined as plaque and media cross-sectional area divided by external elastic membrane cross-sectional area $\times 100$. A coronary lesion was defined as a segment with a plaque burden of more than 40% in at least 3 consecutive frames. The composition of the atherosclerotic lesions was characterized into 4 different tissue types with the use of IVUS virtual histology (IVUS-VH): fibrous, fibro-fatty, dense calcium and necrotic core. Three types of high-risk lesions were identified: 1. Virtual histology-based thin-cap fibroatheroma (VH-TCFA) lesions, defined as a lesion with presence of >10% confluent necrotic core in direct contact with the lumen; 2. lesions with a plaque burden of $\geq 70\%$; 3. lesions with a minimal luminal area of $\leq 4.0 \text{ mm}^2$ [12,13]. VH-TCFAs were further classified as having a high lesional plaque volume in case the plaque volume of that particular VH-TCFA was above the median plaque volume of all lesions classified as VH-TCFA.

2.4. Statistical analysis

Normally distributed continuous variables are presented as mean \pm standard deviation (SD). Non-normally distributed continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented in numbers and percentages. Linear regression was used to evaluate the association between segmental plaque volume, plaque burden, plaque tissue types and natural logarithm (ln)-transformed hsTnT concentration (ln-transformation was performed in order to maintain homogeneity of variance and normality of the (error) distribution). Segmental plaque and vessel volume were normalised for the imaged segment length (normalised plaque volume = plaque volume/imaged segment length * median segment length of study population). Logistic regression was used to examine the association between hsTnT concentration and presence of high-risk coronary lesions (as dependent). Determinants of a hsTnT concentration above the clinically used 99th percentile in an apparently healthy reference population of 14 pg/mL [11], were also assessed with logistic regression. Multivariable analyses accounted for confounding by age, gender, hypercholesterolemia, diabetes, glomerular filtration rate, hypertension, smoking status, family history of CAD, history of MI, prior PCI, prior coronary artery bypass grafting (CABG), stroke and peripheral artery disease (PAD). Crude and adjusted odds ratios (OR) are presented with 95% confidence intervals. When necessary to assure parsimony of the logistic regression models, adjustment according to a propensity score (using the same confounders as mentioned above) was used [14,15]. All statistical tests were two-sided with a type I error level of 0.05. Analyses were performed with IBM SPSS statistics version 21.0.

3. Results

Between October 24, 2008 and January 28, 2011, a total of 231 patients with stable angina pectoris were enrolled prior to coronary

angiography. Mean age was 63.6 ± 9.9 years. Men constituted 77% of the study population. A PCI was performed in 85% of the patients during the index coronary angiography (Table 1).

Troponin T was detectable in 5.8% of the study patients by the conventional TnT assay ($>0.01 \mu\text{g/L}$). In contrast, the hsTnT assay enabled detection ($>3 \text{ pg/mL}$) in 212 patients (92%) and concentrations above the commonly used 99th percentile of a healthy reference population of 14 pg/mL were observed in 45 (19.5%) of our patients with manifest stable CAD. The 99th percentile in our patient population was 88.7 pg/mL (Table 1 and Fig. 1).

3.1. Clinical determinants of high-sensitivity Troponin T concentration

Age was the only determinant of hsTnT concentration (adjusted (adj.) $p < 0.001$) (Fig. 2). There was no association with hsTnT concentration and other baseline clinical variables, such as male gender (adj. $p = 0.39$), hypercholesterolemia (adj. $p = 0.28$), diabetes (adj. $p = 0.96$), glomerular filtration rate (adj. $p = 0.08$), hypertension (adj. $p = 0.64$), smoking status (adj. $p = 0.37$), family history (adj. $p = 0.60$), history of MI (adj. $p = 0.57$), PCI (adj. $p = 0.60$), CABG (adj. $p = 0.46$), stroke (adj. $p = 0.61$), or PAD (adj. $p = 0.28$), and the number of diseased coronary vessels on angiography (adj. $p = 0.71$).

Table 1
Baseline characteristics.

Patient characteristics, N (%)	N = 231
Age (years \pm SD)	63.6 ± 9.9
Male	177 (76.6)
Diabetes Mellitus	48 (20.8)
Hypertension	141 (61.0)
Hypercholesterolemia	162 (70.1)
Smoking	42 (18.2)
Positive family history of CAD	137 (59.3)
Previous MI	93 (40.3)
Previous PCI	116 (50.2)
Previous CABG	7 (3.0)
Previous stroke	13 (5.6)
Peripheral artery disease	19 (8.2)
Glomerular Filtration Rate (ml/min, median [IQR])	101.5 [80.2–123.0]
Out-patient clinic medication prior to angiography	
Aspirin	218 (94.4)
Beta-blockers	181 (78.4)
ACE-inhibitors	139 (60.2)
Calcium antagonists	63 (27.3)
Oral nitrates	82 (35.5)
Statin	209 (90.5)
High-sensitivity Troponin T levels (pg/mL)	
Median [IQR]	7.3 [4.9–12.1]
Mean	11.0
Standard deviation	15.5
Range	3.00–192.70
99th percentile	88.7
Procedural characteristics	
Extent of coronary artery disease	
No significant stenosis	22 (9.5)
1-vessel disease	116 (50.2)
2-vessel disease	70 (30.3)
3-vessel disease	23 (10.0)
PCI/stent implantation	196 (84.8)
IVUS segment characteristics	
Imaged coronary artery	
Left anterior descending	76 (33.9)
Left circumflex	76 (32.9)
Right coronary artery	79 (34.2)
Segment length, mm [IQR]	43.8 [33.9–56.0]

MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft.

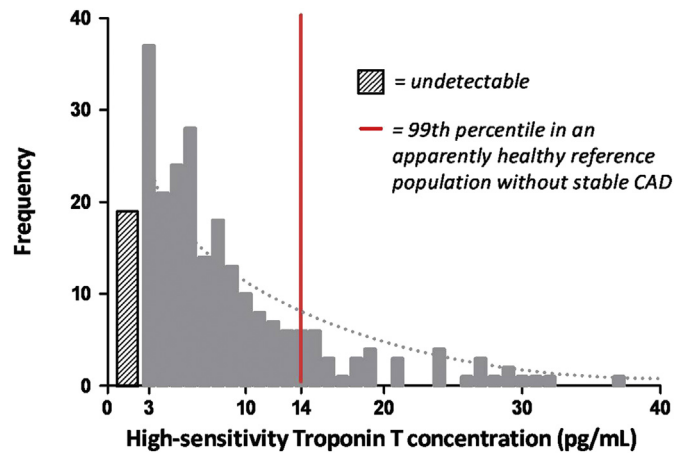


Fig. 1. Distribution of high-sensitivity Troponin T values in patients with stable coronary artery disease. High-sensitivity Troponin T was measured in 231 patients with stable coronary artery disease, undergoing an elective CAG. Blood samples were drawn prior to catheterisation and/or PCI. Troponin concentrations were undetectably low in 19 patients (8.2%). The datapoints of three patients with concentrations of 82, 91 and 192 pg/mL respectively are not shown in this histogram.

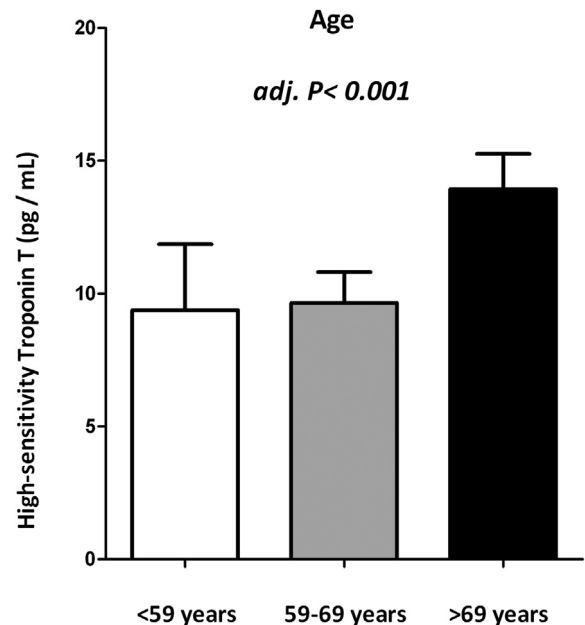


Fig. 2. Age in relation to high-sensitivity Troponin T concentration. The study population was divided in age tertiles of 77 patients each. Multivariable analyses accounted for confounding by age, gender, hypercholesterolemia, diabetes, glomerular filtration rate, hypertension, smoking status, family history of CAD, history of MI, prior PCI, prior coronary artery bypass grafting, prior stroke and peripheral artery disease. The histograms display the mean hsTnT concentration plus the standard error of the mean.

3.2. High-sensitivity Troponin T in association with segmental plaque characteristics

The median segment length, as imaged with IVUS, was 43.8 mm (Table 1). Normalised segmental plaque volumes were positively associated with hsTnT levels (adjusted $\beta = 25.0 \text{ mm}^3$ increase in segmental plaque volume per SD increase in natural log-transformed hsTnT, 95% CI: 6.0–44.0, $p = 0.010$) (Table 2, Fig. 3 A). There was no significant association between segmental plaque burden and hsTnT (adjusted $\beta = 0.92\%$ increase in plaque

Table 2

High-sensitivity Troponin T concentration in relation to plaque characteristics in a non-culprit coronary artery in patients with stable coronary artery disease.

	Total study population	hsTnT <14 pg/mL (N = 186)	hsTnT ≥14 pg/mL (N = 45)	Adjusted P-value
Segmental plaque characteristics				
Median [IQR]				
Normalised vessel volume (mm ³)	563.9 [439.2–755.0]	545.5 [421.2–691.3]	733.6 [494.8–917.5]	0.001
Normalised plaque volume (mm ³)	234.0 [149.9–340.6]	215.2 [140.8–311.2]	271.1 [192.4–413.7]	0.008
Plaque burden (%)	40.4 [32.2–47.7]	39.8 [31.9–47.1]	43.2 [33.8–50.2]	0.41
Plaque composition				
Median [IQR]				
Fibrous (%)	56.3 [49.4–63.8]	56.0 [49.5–65.1]	56.6 [48.6–60.3]	0.49
Fibro-fatty (%)	9.5 [6.3–13.4]	9.3 [5.8–13.4]	11.2 [8.1–14.2]	0.18
Dense calcium (%)	11.0 [5.9–16.1]	10.9 [5.7–16.1]	11.4 [6.3–17.1]	0.79
Necrotic core (%)	21.5 [17.2–25.3]	21.5 [16.7–25.7]	21.5 [18.4–24.9]	0.82
Lesion morphology				
N (%)				
VH-TCFA	86 (37.2)	64 (34.4)	22 (48.9)	0.024
VH-TCFA with high lesional plaque volume	43 (18.6)	28 (15.1)	15 (33.3)	0.005
MLA ≤ 4.0 mm ²	80 (34.6)	67 (36.0)	13 (28.9)	0.66
Plaque burden ≥ 70%	56 (24.2)	41 (22.0)	15 (33.3)	0.064

VH-TCFAs were classified as having a high lesional plaque volume in case the plaque volume of that particular VH-TCFA was above the median of all lesions classified as VH-TCFA. Multivariable analyses accounted for confounding by age, gender, hypercholesterolemia, diabetes, glomerular filtration rate, hypertension, smoking status, family history of CAD, history of MI, prior PCI, coronary artery bypass grafting, stroke and peripheral artery disease (PAD).

HsTnT = high-sensitivity Troponin T; VH-TCFA = Virtual histology-derived Thin-cap fibroatheroma; MLA = minimal luminal area.

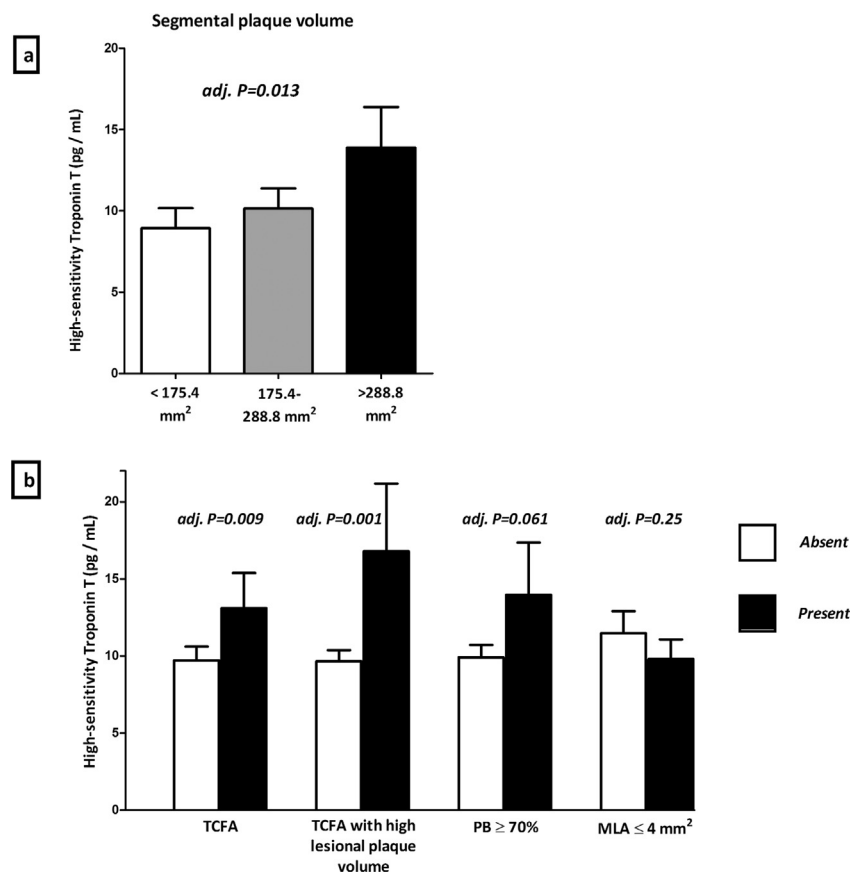


Fig. 3. High-sensitivity Troponin T concentration in relation to intravascular ultrasound characteristics. HsTnT, high-sensitivity Troponin T; PB, plaque burden; MLA, minimal luminal area; VH-TCFA, Virtual histology-derived thin-cap fibroatheroma. **Panel A.** High-sensitivity Troponin T per tertile of normalised plaque volume for the entire segment (median length 43.8 mm, IQR: 33.9–56.0) as evaluated with grayscale intravascular ultrasonography (IVUS). **Panel B.** High-sensitivity Troponin T in relation to the presence of at least one high-risk lesion type per patient. Thin-cap fibroatheroma (TCFA) was assessed by means of radiofrequency IVUS. VH-TCFAs were classified as having a high lesional plaque volume in case the plaque volume of that particular VH-TCFA was above the median plaque volume of all lesions classified as VH-TCFA. For both figures, multivariable analyses accounted for confounding by age, gender, hypercholesterolemia, diabetes, glomerular filtration rate, hypertension, smoking status, family history of CAD, history of MI, prior PCI, coronary artery bypass grafting, stroke and peripheral artery disease. The histograms display the mean hsTnT concentration plus the standard error of the mean.

burden per SD increase in natural log-transformed hsTnT, 95% CI: –0.61 to 2.44, $p = 0.24$). However normalised segmental vessel volumes were positively associated with hsTnT levels (adjusted $\beta = 56.2 \text{ mm}^3$ increase in segmental vessel volume per SD increase

in natural log-transformed hsTnT, 95% CI: 21.9–90.5, $p = 0.001$).

High-sensitivity Troponin T concentrations were not associated with the segmental plaque distribution of the four tissue types as assessed by IVUS virtual histology; fibrous (adj. $p = 0.81$), fibro-

fatty (adj. $p = 0.66$), dense calcium (adj. $p = 0.37$) and necrotic core (adj. $p = 0.80$).

3.3. High-sensitivity Troponin T in association with lesion characteristics and morphology

With respect to lesion morphology, a VH-TCFA was observed in 86 (37%) patients (Table 2 and Supplementary appendix – Fig. 4). Higher hsTnT levels were measured in patients with the presence of a VH-TCFA (adj. OR for presence of VH-TCFA = 1.52 per SD increase in natural log-transformed hsTnT, 95% CI: 1.10–2.11, $p = 0.011$) (Fig. 3B).

In patients with hsTnT concentrations ≥ 14 pg/mL, a VH-TCFA was observed in 49%. Hence, patients with a VH-TCFA had a 2-fold increased prevalence of hsTnT concentration ≥ 14 pg/mL (adj. OR 2.35, 95% CI: 1.12–4.91, $p = 0.024$) (Table 2). In addition, a 3-fold increased prevalence of hsTnT concentration ≥ 14 pg/mL was observed in patients with a VH-TCFA with a high lesional plaque volume, i.e. a lesional plaque volume above the median of all lesions classified as VH-TCFA (adj. OR 3.36, 95% CI: 1.44–7.84, $p = 0.005$) (Table 2). Patients with a VH-TCFA with a high lesional plaque volume also had higher hsTnT levels than patients with a VH-TCFA without a high lesional plaque volume (16.8 pg/mL versus 9.4 pg/mL, $p = 0.03$).

The relationship between lesions with a plaque burden $\geq 70\%$ and hsTnT was not statistically significant (adj. OR = 1.37 per SD increase in natural log-transformed hsTnT, 95% CI: 0.99–1.90, $p = 0.059$) (Table 2 and Fig. 3B). No association was found between lesions with a MLA ≤ 4.0 mm² and hsTnT (adj. OR = 0.83 per SD increase in natural log-transformed hsTnT, 95% CI: 0.60–1.15, $p = 0.26$).

4. Discussion

This cross-sectional study is the first to demonstrate an association between elevated circulating Troponin levels and the extent of coronary atherosclerosis and high-risk plaque phenotypes, as assessed with intracoronary IVUS in a non-culprit coronary artery in a broad population of stable CAD patients referred for elective coronary angiography, as seen in everyday routine clinical practice.

In contrast to the conventional TnT assay, the hsTnT assay has enabled detection of circulating TnT in the majority of patients with stable CAD. Our finding that serum TnT levels were detectable in only 5.8% of our stable CAD patients with the conventional fourth generation TnT assay, versus detection in 92% when using the hsTnT assay, corresponds to the results found in the Heart and Soul study [3]. This expansion of serum TnT detection has led to more elaborate risk prediction for the occurrence of MACE, as previously demonstrated [3,4,6,16]. In a post-hoc analysis of the relatively low-risk, stable CAD population of the PEACE trial, a graded increase in the cumulative incidence of cardiovascular death (adjusted hazard ratio (HR) per unit increase in the natural logarithm of the hsTnT level 2.09; 95% confidence interval [CI], 1.60 to 2.74) and of heart failure (adjusted HR 2.20; 95% CI, 1.66 to 2.90) was seen in 3679 patients with stable CAD and preserved left ventricular function [4]. Similarly hsTnT was an independent predictor of death from cardiovascular causes, myocardial infarction, or stroke in patients who had both type 2 diabetes and stable ischemic heart disease in a post-hoc analysis of the BARI-2D trial [5]. In addition, several prospective, intracoronary imaging studies, primarily conducted in ACS-patients, have reported an increased risk of repeat MACE in the presence of TCFA as identified by IVUS-VH [17,18]. The presence of a VH-TCFA was associated with a 3-fold increased risk of cardiovascular mortality, cardiac arrest, MI, or rehospitalization due to unstable or progressive angina during 3.4 year follow-up of ACS

patients enrolled in the PROSPECT study [17]. More recently, similar conclusions were drawn with respect to the complete ATHEROREMO-IVUS study population comprising both stable CAD and ACS patients [9]. The presence of a VH-TCFA, in a single target segment without significant luminal narrowing in a non-culprit coronary artery, was independently associated with the composite of death and non-fatal ACS (7.5% vs. 3.0%; adjusted HR 2.51, 95% CI 1.15–5.49) during 1-year follow-up [9].

Thus, both TnT elevation and high-risk intracoronary lesion phenotypes as assessed by radiofrequency IVUS are recognized as independent predictors of adverse cardiovascular outcome. Yet, to our best knowledge, this is the first study to describe the crosslink between TnT elevation and the extent and phenotype of coronary atherosclerosis as assessed by IVUS in a non-culprit coronary artery in a population of patients with stable CAD.

Despite the increasing body of evidence showing adverse outcome in case of Troponin elevation in ambulatory non-ACS patients, only few reports have actually provided insight into a possible mechanistic explanation for the Troponin elevation from the perspective of coronary pathophysiology. A greater insight into the pathophysiological mechanisms of Troponin elevation may also increase our understanding of how Troponin elevation is linked to adverse outcome in this patient population. In two studies evaluating cardiac computed tomography, one in patients with stable CAD and another in patients with acute chest pain presenting at the emergency department, hsTnT levels were not associated with stenosis severity, but were associated with the extent of coronary plaque volume, which might support the hypothesis that chronic, clinically silent rupture or erosion of non-calcified plaques with subsequent microembolisation may be a potential source of myocardial injury and Troponin release [19,20]. However, given the current state-of-the-art, cardiac computed tomography does not allow for such extensive plaque phenotyping as grayscale and radiofrequency IVUS. Therefore, our data showing that VH-TCFAs are associated with Troponin release are essential for the line of reasoning and hypothesis that microembolisation resulting from silent plaque rupture or erosion might be a possible mechanistic explanation for the elevated Troponin levels in these patients. Indeed, autopsy studies have described TCFAs to be the plaques that are most prone to superficial erosion or rupture, consequently leading to thrombus formation and distal (micro)embolisation [21]. Such plaque erosion or rupture has shown to be the major cause of (fatal) acute MI, but not every plaque erosion or rupture invariably leads to sufficient thrombotic occlusion in order to provoke symptoms of angina. It has been suggested that, at any given time, approximately 15% of patients with stable CAD have ongoing atherothrombotic plaque events compared to an annual incidence of acute MI of approximately 5% [22]. Against this background, hsTnT may serve as a biomarker for subclinical plaque rupture or erosion leading to atherothrombosis, distal embolisation and continuous low grade myocardial ischemia and cardiomyocyte necrosis, even in presumably asymptomatic patients with stable CAD.

Similarly, the association between the presence of VH-TCFA and serum TnT elevation as found in the current population might also be extended in order to hypothesize on the observation of subtle TnT elevation in the general population and the associated increased risk of MACE. In the Dallas Heart Study, a multi-ethnic, population-based cohort study of individuals aged 30–65 years, the prevalence of TnT levels above 3.0 pg/mL was 25.0% [16]. Interestingly, a graded increase in both cardiovascular and all-cause mortality was seen across quintiles of TnT elevation in the entire study cohort, but also in the subgroup analysis of 3222 patients without cardiovascular or chronic kidney disease. A five-fold increased risk for cardiovascular mortality was observed in case

of hsTnT levels ≥ 14 pg/mL. Understandably, the Dallas Heart study did not collect intracoronary IVUS data. Although speculative, an increased prevalence of rupture-prone, high-risk lesion types, such as TCFAs, might underlie the observation that participants without symptoms of angina, i.e. without a fixed and significant coronary luminal narrowing, did have both TnT elevation and a subsequent increased risk of cardiovascular mortality.

Another important finding of our study was the association between segmental plaque volume and Troponin concentration. Similar observations were previously found in cardiac computed tomography studies [19,20]. More recently, a post-hoc analysis of the SATURN trial has demonstrated that a large plaque volume as assessed with grayscale IVUS, in a non-culprit segment without significant stenosis, is associated with increased risk of MACE [23]. Hence, segmental plaque volume of a non-culprit coronary artery, as assessed in ATHEROREMO-IVUS, may have prognostic importance. Segmental plaque volume may not only be linked to Troponin concentration, but also to TCFA and plaque rupture, since the majority of large stable plaques have evidence of previously healed plaque rupture with incorporation of old thrombus into the atheroma [21,22,24,25].

Troponin was not related to segmental plaque burden ($p = 0.24$). Levels seemed higher in patients with a lesion with plaque burden $\geq 70\%$, but the difference with patients with smaller plaque burden did not reach statistical significance ($p = 0.061$). This may be due to the fact that plaque burden is not a direct measure of three dimensional plaque volume, but rather a two dimensional measure that also accounts for arterial wall remodeling. The fact that both normalized plaque and vessel volume were highly associated with troponin levels may be seen as a confirmation of positive remodeling in our dataset. Outward remodeling explains why presence of large segmental plaque volumes do not necessarily relate to focal lesional stenoses. The observation that stenosis severity, i.e. a MLA ≤ 4.0 mm², was not related to hsTnT concentration in our study may be regarded as a reconfirmation of the earlier mentioned cardiac computed tomography studies [19,20,26]. Similarly, coronary artery calciumscore was not associated with hsTnT concentration after multivariate adjustment in the Dallas Heart Study [16]. Such observations may indirectly support the hypothesis that not ischemia due to luminal narrowing, but rather plaque rupture, microembolisation and microcirculatory dysfunction is the pathophysiological mechanism behind the increased circulating TnT levels [27]. On the other hand, it has to be emphasized that 84.8% of the patients in our analysis underwent a PCI and therefore had significant luminal stenosis in the culprit vessel. Our protocol was based on non-culprit, single vessel imaging. Since the culprit vessels were not imaged, all of our associations only apply to the angiographically non-stenotic non-culprit segments and no formal conclusions can be drawn on stenosis severity elsewhere in the coronary circulation and Troponin elevation.

Our study has several strengths. Our data were prospectively obtained and, due to the broad inclusion criteria of ATHEROREMO-IVUS, its conclusions seem applicable to a broad range of patients with stable CAD. Of great importance is that IVUS evaluation was performed in an independent, dedicated core lab with personnel blinded for patient and TnT data. Similarly, Troponin was measured by laboratory personnel blinded for baseline patient characteristics and IVUS data.

4.1. Study limitations

However, there are several limitations to our findings. A possible limitation of our analysis might be the sample size, although this study represents the only and therefore largest cohort of patients in which the association between intracoronary IVUS plaque

characteristics and circulating hsTnT was evaluated, so far. Furthermore, ATHEROREMO-IVUS was a single center study by virtue of design. External validation, preferably in a larger sample size, is a fundamental prerequisite before final conclusions may be drawn. In our study, IVUS imaging took place of a pre-specified single target segment of a non-culprit coronary artery of least 40 mm in length and without significant luminal narrowing ($<50\%$ stenosis) as assessed by on-line angiography. This approach was developed under the assumption that such a non-stenotic segment would adequately reflect coronary wall pathophysiology of the larger coronary tree. Indeed, in a previous ATHEROREMO-IVUS report, this assumption was confirmed with respect to the presence of high-risk lesion types, such as VH-TCFA, and subsequent increased risk of MACE [9]. In addition, the post-hoc analysis of the SATURN trial also emphasized the prognostic importance of plaque characteristics of a non-stenotic, non-culprit target segment [23]. Ideally, a confirmatory replication of our association between segmental plaque volume, presence of (VH-)TCFA and TnT elevation should take place in a study enrolling patients with stable CAD for three-vessel and left main IVUS assessment, since such an approach would more precisely characterize the total coronary atherosclerosis burden. IVUS-VH has been validated *in vitro* [28]. Sensitivities and specificities for the detection of various plaque components ranged from 72 to 99%, thus leaving room for misclassification [28]. Furthermore, its ability to detect plaque erosion, rupture and thrombus is limited given the current spatial resolution.

In conclusion, plaque volume and presence of VH-TCFAs, as assessed with intracoronary IVUS in a non-culprit coronary artery segment, are associated with higher circulating Troponin concentrations in a broad population of patients with stable CAD. Our data are based on associations and cannot provide final conclusions on the exact etiology of Troponin elevation. However our findings may generate the hypothesis that subclinical plaque rupture or erosion of vulnerable plaques and subsequent intracoronary thrombosis and distal embolisation may be the potential mechanism of action with respect to Troponin elevation and its relation with adverse outcome.

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Conflict of interest

None. There is no commercial association that might pose a conflict of interest in connection with this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.atherosclerosis.2016.02.012>.

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