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RESEARCH LETTER

WILEY

Comparison of high-sensitive cardiac troponin T and I in patients with chronic coronary syndrome

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1 | INTRODUCTION

Patients with chronic coronary syndrome (CCS) represent a heterogeneous group for their risk profiles, clinical manifestations as well as presence of obstructive coronary atherosclerosis, inducible ischemia, and myocardial damage.[1] Cardiac troponins are structural proteins found in the myofibrils of cardiomyocytes and, because of their cardiac specificity, determination of their circulating levels is the keystone for the diagnosis of myocardial injury in patients with suspected acute coronary syndromes.[2] Development of high sensitivity assays has enhanced the ability to detect low circulating levels of cardiac troponin I and T (hs-cTnI and hs-cTnT).[3,4] Elevated hs-cTnT and hs-cTnI plasma concentrations have been associated with adverse cardiovascular outcome in the general population[5,6] and in patients with coronary artery disease (CAD).[7–11] However, in patients with CCS, it is not fully clear whether they are associated with specific risk profiles and disease manifestations, including obstructive CAD and inducible myocardial ischemia, potentially causing chronic myocardial injury.

The present study was aimed at evaluating in a subpopulation of patients with CCS enrolled in the EVINCI study[12] the association between plasma levels of hs-cTnT and hs-cTnI with the patient clinical/molecular risk profiles and with the presence of obstructive CAD at computerized tomography angiography (CTA) and of inducible myocardial ischemia at stress cardiac imaging. The possible role of hs-cTns as independent predictors of adverse cardiovascular events in the same population was also evaluated.

2 | MATERIALS AND METHODS

2.1 | Study design

The EVINCI study (http://www.clinicaltrials.gov, NCT00979199) was performed in patients with CCS, i.e.

with stable chest pain (typical angina, atypical angina or non-anginal), after exclusion of acute coronary syndrome, known CAD, other significant cardiovascular diseases or contraindications to imaging, enrolled prospectively from 14 European centres between March 2009 and June 2012.[12] Each patient underwent CTA and at least one imaging stress test, including single-photon emission computed tomography (SPECT), positron emission tomography (PET), cardiac magnetic resonance (CMR) or echocardiography (Echo) and those who completed the protocol were submitted to follow-up visits until February 2016, where cardiovascular events were recorded.[13] Blood samples were collected before non-invasive imaging and stored in the EVINCI biobank. Ethical approval was provided by each participating centre and all subjects provided written informed consent. Among the 697 patients enrolled in the EVINCI studies, 364 were selected for the present analysis based on availability of CTA, stress images, follow-up data and plasma samples (see Study Flow Chart, Figure S1 of Supplementary Material).

2.2 | Clinical and bio-molecular profile

Risk factors were defined as previously reported.[12–14] Plasma concentrations of cTnT were measured using the hs-cTnT method on COBAS E411 with Elecsys Troponin T hs STAT by Roche Diagnostics (3–5 ng/L LoD; <10% inter-run variation). Plasma concentrations of cTnI were measured using the hs-cTnI method on STAT Architect high Sensitive TnI using the Architect i1000SR platform (Abbott Diagnostics; 1.1–1.9 ng/L LoD; 2.5% intra-run variation; <4% inter-run variation). Additional biomarkers were measured using standard methods.

2.3 | Non-invasive imaging and outcome

The methodology for coronary CTA and for stress myocardial imaging analyses in the EVINCI Outcome study has been previously reported.[13] Briefly, obstructive CAD was defined by the presence of >50% stenosis in at least one major coronary vessel at CTA. The presence of inducible myocardial ischemia was defined by evidence of mild to severe inducible perfusion or wall motion abnormalities at stress imaging. Criteria used to define presence of inducible ischemia at any stress imaging modality are reported elsewhere.[13]

The outcome end-point was composed of cardiac death, non-fatal myocardial infarction, and hospitalization for unstable angina or heart failure.

2.4 | Statistical analysis

Categorical variables are presented as numbers (percentage), continuous variables as mean ± SD. The logarithmic transformation of continuous variables was used when not normally distributed. Differences in continuous variables between two groups were tested using Student's *t* test. Comparisons among groups were performed using ANOVA and Fisher test were used for post-hoc comparisons. Pearson's chi-squared test was used to compare categorical data. Linear regression was used to estimate the effect of clinical characteristics, molecular variables, and presence of obstructive CAD and inducible ischemia on hs-cTns levels, using backward and forward stepwise selections to build up the final model. The ability of the hs-cTns to predict patient outcome was assessed using Kaplan Meier curves and multivariable proportional hazards (Cox) models, adjusting for EuroSCORE, used as a synthetic variable of main clinical risk determinants (Model 1) and for presence of inducible ischemia (Model 2) or obstructive CAD (Model 3) or inducible ischemia and/or obstructive CAD (Model 4–5). This work is a sub-study of the EVINCI study and of the EVINCI outcome study and the sample size calculation was not performed. All analyses were performed using the SPSS 23 software. A two-sided value of $p < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the study population

Baseline characteristics of the study population (364 patients with CCS) are reported in Table 1. The mean age of the study sample was 61 years, and 59% were males. Among cardiovascular risk factors, most of the patients had hypercholesterolaemia (61%) and hypertension (64%). Metabolic and Inflammatory profiles were in the normal range. As to troponins, the median value [25–75 percentile] of hs-cTnT was 6.5 [4.2–9.2] ng/L, of hs-cTnI was 4.4 [2.4–12.4] ng/L. The median values were used as cut-off points to divide patients into groups with low (<median) or high (≥median) concentrations of hs-cTnT and hs-cTnI. Baseline characteristics of the patients are compared between groups in Table S1.

3.2 | hs-cTns and presence of obstructive CAD and inducible ischemia

All patients performed either CTA and at least one stress imaging test. In the whole population, obstructive

TABLE 1 Baseline characteristics of the study population.

Study population ($n = 364$)			
Clinical characteristics		**Molecular profile**	
Demographics		*Myocardial damage*	
Age (years)	61 ± 9	hs-cTnT (ng/L)	8.0 ± 6.2
Male sex	216 (59)	hs-cTnI (ng/L)	55.4 ± 239.6
CV risk factors		*Myocardial function*	
Family history of CAD	124 (34)	NT-proBNP (ng/L)	133.5 ± 220.2
Diabetes mellitus	99 (27)	*Glucose metabolism*	
Hypertension	232 (64)	FPG (mg/dL)	112 ± 36
Hypercholesterolaemia	221 (61)	Insulin (μUI/mL)	11.3 ± 11.2
Obesity	77 (21)	*Lipid metabolism*	
Smoking	80 (22)	Total cholesterol (mg/dL)	180 ± 47
EuroSCORE	.04 ± .03	LDL_C (mg/dL)	103 ± 38
Medications		HD-C (mg/dL)	52 ± 17
Beta-blockers	158 (43)	Triglycerides (mg/dL)	124 ± 77
Calcium antagonists	77 (21)	Apo A1 (mg/dL)	143 ± 32
ACE Inhibitors	102 (28)	Apo B (mg/dL)	86 ± 27
ARBs	71 (19)	Lp (a) (mg/dL)	21.9 ± 24.0
Diuretics	64 (18)	*Inflammation*	
Aspirin	192 (52)	hs-CRP (mg/dL)	.41 ± 1.24
Oral antidiabetics	80 (22)	Interleukin 6 (ng/L)	1.28 ± 2.36
Statins	215 (59)	HO-1 (ng/mL)	5.61 ± 4.31
		Leptin (ng/mL)	10.5 ± 11.1
		Adiponectin (mg/mL)	9.55 ± 6.47

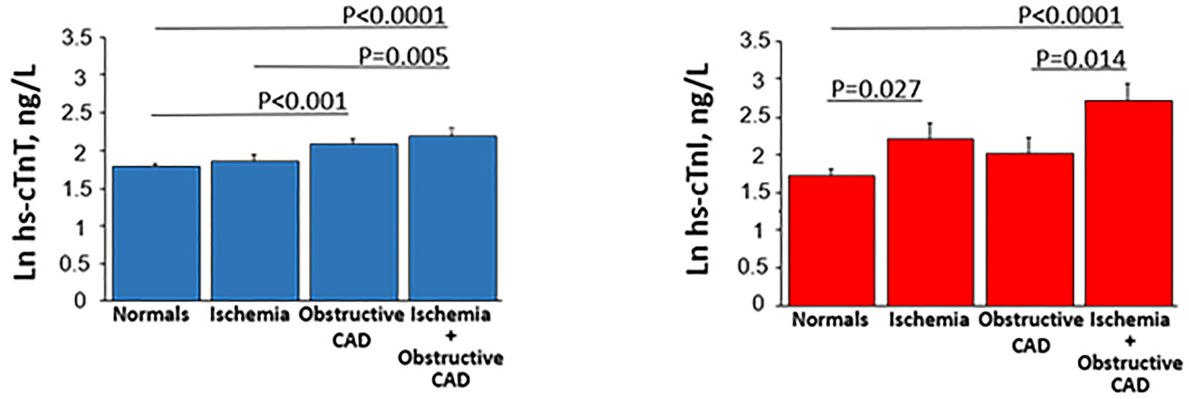
Note: Continuous variables are presented as mean ± standard deviation, categorical variables as absolute N and (%).

CAD was documented at coronary CTA in 107 patients (29%), inducible ischemia at non-invasive stress imaging in 100 patients (27%). In Figure 1A, patients were subdivided into groups according to the presence of inducible ischemia and obstructive CAD, either alone or in combination. Patients with obstructive CAD, showed significantly higher levels of hs-cTnT than patients without obstructive CAD, independently from the presence of ischemia. Patients with inducible ischemia had significantly higher levels of hs-cTnI as compared with patients without ischemia, independently from the presence of obstructive CAD (Figure 1A). At multivariate analysis (Figure 1B), obstructive CAD, together with age, male gender, NT-proBNP, and fasting plasma glucose (FPG) was independently associated with plasma hs-cTnT. On the other hand, inducible ischemia together with HDL-C, triglycerides, Heme Oxigenase-1 (HO-1), and Interleukin-6 was independently associated with hs-cTnI.

3.3 | hs-cTns and patients' outcome

During a median follow up of 4.37 [3.93–5.46] years, 28 patients (8%) had outcome endpoint, including death from any cause (2%), non-fatal myocardial infarction or unstable angina (5%), and hospitalization for heart failure (.3%). Associations of hs-cTnT and hs-cTnI with outcome are shown in Figure 2. At Kaplan–Meier analysis (Figure 2A), either hs-cTnT and hs-cTnI were significantly associated with adverse cardiovascular events. At multivariate Cox analysis (Figure 2B), after correction for age, gender, and risk factors (EuroSCORE) (Model 1), only hs-cTnI remained an independent predictor of cardiovascular events. Further adjustment for presence of inducible ischemia (Model 2), obstructive CAD (Model 3), inducible ischemia or obstructive CAD (Model 4), inducible ischemia and obstructive CAD (Model 5) did not appreciably alter the associations between hs-TnI and outcome.

(A)



(B)

	hs-cTnT		hs-cTnI	
Variables	Coefficient (SE)	P Value	Coefficient (SE)	P Value
Age	0.01 (0.01)	<0.001	---	---
Gender male	0.41 (0.06)	<0.0001	---	---
NT-proBNP	0.12 (0.02)	<0.0001	---	---
FPG	0.35 (0.10)	<0.001	---	---
HDL-C	---	---	-0.88 (0.25)	<0.001
Triglycerides	---	---	0.68 (0.14)	<0.0001
Interleukin-6			0.51 (015)	<0.001
HO-1			0.20 (0.08)	0.009
Obstructive CAD	0.13 (0.06)	0.035	---	---
Inducible ischemia	---	---	0.54 (0.16)	<0.001

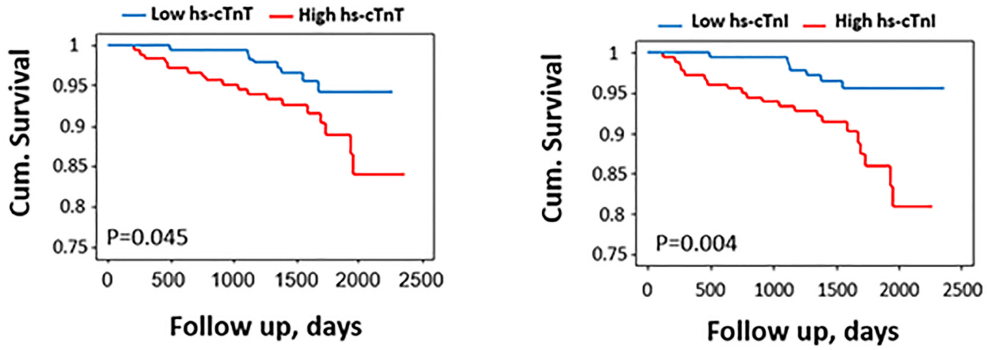
FIGURE 1 (A) hs-cTnT and hs-cTnI plasma levels in patients subdivided in groups according to the presence of inducible ischemia and obstructive CAD, either alone or combined. (B) Predictors of hs-cTnT ans hs-cTnI plasma levels at multivariate analysis.

4 | DISCUSSION

The present study, performed in a well characterized European population of patients with CCS, demonstrated that higher hs-cTnT levels are mainly associated with the presence of obstructive CAD and higher hs-cTnI levels are mainly associated with inducible ischemia, while patients with the most severe condition of obstructive CAD and inducible ischemia have increased levels of both Troponins. Interestingly, only hs-cTnI is an independent predictor of cardiovascular events after adjustment for classical risk factors and presence of coronary disease phenotypes at least in the present population of CCS patients.

In this study, not only distinct imaging phenotypes were predictive of elevated levels of the two Troponins, but also absolutely different molecular profiles (Figure 1). Taken

(A)



(B)

	hs-cTnT		hs-cTnI	
	HR (CI 95%)	P value	HR (CI 95%)	P value
Model 1 Adjusted for EuroSCORE	2.05 (0.87-4.78)	0.099	3.01 (1.31-7.33)	0.010
Model 2 Adjusted for EuroSCORE and inducible ischemia	2.04 (0.86-4.92)	0.103	3.27 (1.35-7.80)	0.010
Model 3 Adjusted for EuroSCORE and obstructive CAD	1.69 (0.71-4.05)	0.236	2.70 (1.13-6.46)	0.025
Model 4 Adjusted for EuroSCORE and inducible ischemia or obstructive CAD	1.53 (0.66-3.55)	0.316	2.67 (1.10-6.44)	0.029
Model 5 Adjusted for EuroSCORE and inducible ischemia and obstructive CAD	1.98 (0.83-4.69)	0.121	3,03 (1.27-7.26)	0.013

FIGURE 2 (A) Kaplan–Meier estimates of the outcome endpoint according to hs-cTnT and hs-cTnI median values; (B) Adjusted Hazard Ratios for events by hs-TnI and hs-TnT median values.

together, these results suggest that different mechanisms may drive troponin I and T release by cardiac muscle in the chronic setting. Plasma levels of hs-cTnT have been shown to associate with the presence of chronic coronary atherosclerosis,[7,8] and this may depend on chronic myocardial damage with myocyte necrosis caused by microembolisms of atherosclerotic and thrombotic material into the microcirculation and/or severe repeated episodes of inducible myocardial ischemia in the presence of obstructive lesions.[7,8,15] Consistently, the well-known risk factors associated with the classical phenotype of obstructive CAD, such as age, male gender, NT-proBNP, and FPG, were the predictors of hs-cTnT.[16] On the other hand, plasma levels cTnI could also reflect the presence of more chronic and less severe ischemia secondary to endothelial dysfunction even in the absence of coronary obstruction.[17] Accordingly, in the present study, higher hs-cTnI levels were found in patients with documented ischemia independently from the presence of obstructive CAD. Interestingly, higher hs-cTnI levels were also associated with features of cardiometabolic risk (high Triglycerides and low HDL-C), inflammation (Inteurlekin-6) and oxidative stress (HO-1), identifying the emerging profile of residual atherosclerotic risk, alternative to the classic risk profile.[14,16,18]

Recent studies have suggested that hs-TnT and hs-TnI concentrations are associated with cardiovascular events in patients with CCS,[8–11] such as in this study. However, after adjustment for classical cardiovascular risk factors, presence of obstructive CAD and/or inducible ischemia, hs-TnI, but not hs-TnT, remained independently associated with outcome. A different association of hs-TnT and hs-TnI with cardiovascular outcome has been previously reported in patients with CAD[7] and in community-based studies, primarily in patients without prevalent CVD.[5,6] In these studies, the result that only hsTnI, but not hs-cTnT, was a strong predictor of cardiovascular events, including also heart failure, was explained considering a noncardiac expression, a racial component, specific genetic determinants, and methodological issues, suggesting for hsTnI a superiority as a more specific marker of cardiovascular disease. In the present study, the differences in outcome prediction could be explained considering the different molecular profiles associated with the two troponins. In particular, the molecular pathways such as altered lipid metabolism and inflammation/oxidative stress, associated high hs-cTnI plasma concentration, could be responsible for the significant ability of hs-cTnI to predict adverse outcome in a population of CCS patients.

5 | CONCLUSION

The present findings suggest that elevation of plasma levels of hs-cTnT and hs-cTnI are differentially associated with the presence of obstructive coronary atherosclerosis or inducible myocardial ischemia. In the present population of patients of CCS, hs-TnI is also an independent predictor of outcome beyond CAD phenotypes. Further studies could be needed to assess whether these observations might have clinical implications.

AUTHOR CONTRIBUTIONS

Conceptualization: CC. Data curation and investigation: CC, RR, RL, CP. Formal analysis, funding acquisition, and writing - original draft: CC, DN. Supervision AG, AS, JK, AC, DN. Writing - review & editing: RR, RL, CP, AG, AS, JK, AC.

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CONFLICT OF INTEREST STATEMENT

None declared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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