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Hs-cTroponins for the prediction of recurrent cardiovascular events in patients with established CHD – A comparative analysis from the KAROLA study

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ABSTRACT

Background: High-sensitivity Troponins (hs-cTnT and hs-cTnI) are established biomarkers to identify patients with an acute myocardial infarction. However, data comparing the capacity of these two subtypes in predicting recurrent cardiovascular disease (CVD) events in a population with stable coronary heart disease (CHD) after adjustment for several other modern biomarkers are lacking.
Methods: We measured both troponins at baseline in 1068 CHD patients, followed them for 13 years, assessed a combined CVD endpoint, and adjusted for multiple traditional and novel risk factors.
Results: Both troponins correlated significantly with age, low and high BMI, male gender, statin therapy, and emerging biomarkers (e.g. cystatin C, NT-proBNP, GDF-15, hsCRP or galectin 3). During follow-up of 13 years, 267 fatal and non-fatal CVD events occurred. Top quartiles of both troponin concentrations were significantly associated with CVD events compared to the bottom quartile after adjustment for age, gender and established CVD risk factors (hs-cTnT: hazard ratio (HR) 2.54 (95% CI, 1.60–4.03), p for trend: <0.0001; hs-cTnI: HR 2.20 (95% CI, 1.44–3.36), p for trend: <0.0002 and 0.0003). However, after adjustment for other emerging biomarkers, the associations were no longer statistically significant (hs-cTnT: HR 1.63 (95% CI, 0.97–2.73), p for trend: 0.17; hs-cTnI: HR 1.61 (95% CI, 1.00–2.60), p for trend: 0.067).
Conclusion: Both troponins are reliable biomarkers of recurrent cardiovascular events, especially if other novel, important markers such as NT-proBNP, GDF-15 and galectin 3 are not available. Nevertheless, a further workup is still needed to explain the complex interaction of biomarkers indicating vascular and myocardial function.

1. Introduction

In the setting of acute coronary syndrome (ACS), cardiac troponins have been established for many years to reliably identify patients suffering from an acute myocardial infarction (MI) [1]. Moreover, elevated troponin concentrations are strongly associated with prognosis in such patients and guide the way for therapeutic interventions [2]. In addition to standard troponins, high-sensitivity troponin (hs-cTnT and hs-cTnI) assays have become frequently available to further increase the accuracy of diagnosing myocardial necrosis as the most common cause of elevated troponin concentrations. Indeed, several reports confirmed the ability of these hs assays to detect myocardial injuries in a very early stage [3–6].

Moreover, these very low and by conventional assays not quantifiable troponin concentrations are associated with unfavourable outcomes such as coronary heart disease (CHD), incident heart failure, and mortality in primary prevention settings [7–9]. Besides the important role of identifying patients at risk for an acute event, the status of hs-troponins predicting recurrent cardiovascular events in patients with stable CHD deserves attention. Despite optimal medical and interventional therapies, the recurrence rates in patients who survived an acute coronary event are still high [10]. Hence, diagnostic tools such as biomarkers, which can be easily ascertained, are required to identify

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individuals at high risk. Cardiac hs-cTnI is exclusively expressed in the myocardium, whereas expression of hs-cTnT isoforms has been described in skeletal muscle also and may lead to cross-reactivity. Therefore, the accuracy of the two troponins might be different and as a result, the prognostic value too [11]. Previous studies analysed both troponin subtypes (T and I) separately of each other [10,12,13]. However, a direct comparison of these important biomarkers within one well-characterised cohort followed for many years is still missing but might further elucidate the prognostic value of these proteins. We thus analysed the prognostic value of hs-cTnT and hs-cTnI for recurrent cardiovascular disease (CVD)-events within the KAROLA study and adjusted for multiple established and novel risk markers.

2. Materials and methods

2.1. Study population

As reported in previous publications [10,14–16], the KAROLA study was initiated to elucidate the long-term course of patients who either experienced an acute cardiovascular event (e.g. myocardial infarction (MI)) or underwent an elective coronary artery bypass (CABG) surgery or percutaneous coronary intervention (PCI) between January 1999 and May 2000. Patients (aged between 30 and 70 years, meeting the ICD-9 criteria (codes 410-414) for CHD) suffering from one of the above mentioned conditions for the first time took part in a 3-week rehabilitation program in two collaborating rehabilitation clinics in Germany (*Schwabenland-Klinik*, Isny, and *Klinik im Südpark*, Bad Nauheim). The aim of this rehabilitation program, which is usually being offered to such patients in Germany, is defined as to prevent early retirement of the young and nursing dependency of the elderly. In general, rehabilitation programs start right after the acute-care-hospital stay. In our cohort we recruited patients who have started their individual program within the first 3 months after their acute event.

All patients gave their written consent to participate in the study. As reported previously [10,16], the study was approved by the ethics committees of the Universities of Ulm and Heidelberg, and by the ethics boards of the chambers of physicians of the federal states of Hessen and Baden-Wuerttemberg.

2.2. Data collection

In all patients, active follow-up was conducted 1, 3, 4.5, 6, 8, 10 and 13 years after having completed the 3-week rehabilitation program at baseline. Information regarding secondary cardiovascular events and treatment since discharge was obtained from the primary care physician by means of a standardized questionnaire. Furthermore, we asked the primary care physician within this questionnaire to obtain specific information on potential secondary CVD events [10,16].

In case a participant had died during follow-up, the underlying cause was obtained from the official death certificate, which can be accessed at the local health authorities, and was documented according to ICD-9 codes 390-459 and ICD-10 codes I0-I99 and R.57.0 [10,16]. Secondary CVD events were defined as the following: CVD as the main cause of death (i.e., ICD-9 codes 390-459 up to year 4.5 follow-up and ICD-10 codes I00-I99 and R57.0 thereafter) and non-fatal stroke or MI as obtained from the primary care physicians [10,16].

2.3. Laboratory methods

All laboratory measurements were based on blood drawings at the time of discharge from the rehabilitation clinic. Standard laboratory parameters (leucocyte count, creatinine and blood lipids) were taken from the charts at the two cooperating rehabilitation clinics. Blood samples were stored at −80 °C for further measurements later on. As reported previously [10], all hs-cTnT measurements were performed with a hs assay by Roche Diagnostics on an Elecsys 2010 platform (Roche) and were performed between January and March 2013. At that time the samples had underwent one freeze-thaw cycle before analysis. The inter-assay CVs were 3.6% and 2.9% at concentrations of 42 and 2.82 ng/L, respectively. Hs-TnI was determined on an Abbott ARCHITECT i1000 with inter-assays of CV being between 5.9 and 6.7 ng/L at 3 different concentrations. Other emerging biomarkers like NT-proBNP, hs C-reactive protein, cystatin C, or galectin-3 were measured as reported previously [10,16].

2.4. Statistical methods

The study population was described with respect to various sociodemographic and medical characteristics. The associations of sociodemographic characteristics, various cardiovascular risk factors, and distributions of biomarkers with troponin concentrations were quantified by means of the nonparametric Kruskal-Wallis test. Partial Spearman correlation coefficients, adjusted for age and gender, were calculated for troponin concentrations and various biomarkers.

To assess the association between log-transformed (ln) hs-cTnT, hs-cTnI, and secondary cardiovascular events, we used the life-table and the Kaplan-Meier method. Modelling with Cox-proportional hazards regression analysis was applied to describe the independent association between hs-cTnT, hs-cTnI, and secondary cardiovascular events. Since our aim was to analyse independent associations between the biomarkers under investigation and recurrent cardiovascular events, we adjusted for potential confounders in a two-step model. First, we included multiple socioeconomic and known cardiovascular risk factors such as body mass index (BMI), smoking status (never, current, former smoker), duration of school education (<10 years, ≥10 years), hospital site (Isny, Bad Nauheim), family status (married, other), history of MI (yes, no), history of hypertension (yes, no), history of diabetes (yes, no), severity of CHD (number of affected epicardial coronary vessels at baseline), initial management of CHD (PCI (yes, no)), intake of β-blockers (yes, no), intake of angiotensin-converting enzyme inhibitors (ACE inhibitors) (yes, no), intake of diuretics (yes, no), intake of lipid lowering drugs (yes, no), HDL cholesterol and LDL cholesterol. Also, we adjusted for eGFR (CKD-EPI cystatin C equation). To avoid over-adjustment, we excluded those factors, which had neither significant influence on secondary events (at an α-level of 0.1) nor changed hs-cTnT or hs-cTnI point estimates in a relevant way (i.e. by >10%) in a manual backward selection. In the second step, we took NT-proBNP, galectin-3 and GDF-15 as further emerging biomarkers into account. Measures of model fit, discrimination, reclassification and calibration were assessed with Cox-proportional hazards regression. The net reclassification improvement (NRI) by adding hs-cTnT or hs-cTnI, respectively was calculated according to the risk strata of 5%, 10% and >20% of predicted probability for an event. Furthermore, the integrated discrimination improvement (IDI) was assessed which estimates the extended model's improvement in the difference in predicted probabilities between cases and non-cases [17,18]. We also used a spline regression (with 4 degrees of freedom) for multivariate analysis. All statistical procedures were performed with the SAS statistical software package (release 9.4 SAS Institute Inc.).

3. Results

3.1. Demographic, clinical and laboratory characteristics

Table 1 displays the sociodemographic, clinical and laboratory characteristics in 1068 patients participating in the KAROLA study. While most individuals were male (85%), the mean age was 58.9 years. The majority of patients had a history of smoking (ex and current 69%), while 184 patients (17%) had diabetes. More than half of the patients suffered from a myocardial infarction (58%). The angiographic evaluation of the coronary status revealed 453 patients (42.4%) with a 3-vessel disease mirroring the severity of disease within this cohort.

Table 1
Sociodemographic, clinical, and laboratory characteristics in 1068 patients with clinically manifest coronary heart disease.

Characteristics at baseline	
Age (years) (μ, SD)	58.9 ± 8.0
Men, n (%)	906 (84.8%)
School education < 10 years, n (%)	638 (59.7%)
Body mass index (kg/m^2), (μ, SD)	26.9 ± 3.3
Smoking status	
– Never	336 (31.5%)
– Ex	679 (63.6%)
– Current	53 (5.0%)
History of diabetes, n (%)	184 (17.2%)
History of hypertension, n (%)	590 (55.2%)
History of myocardial infarction, n (%)	624 (58.4%)
History of heart failure, n (%)	131 (12.7%)
Clinical score (angiographic evaluation)	
– 1 vessel disease	261 (24.4%)
– 2 vessel disease	286 (26.8%)
– 3 vessel disease	453 (42.4%)
– Unknown	53 (5.0%)
PCI	414 (38.9%)
Total cholesterol (mg/dL) (μ, SD)	169.6 (33.1)
LDL-cholesterol (mg/dL) (μ, SD)	101.2 (29.6)
HDL-cholesterol (mg/dL) (μ, SD)	39.4 (10.4)
C-reactive protein (mg/L)[a]	3.48 (1.25; 8.30)
Cystatin C (mg/L)[a]	1.03 (0.93; 1.18)
NT-proBNP (pg/mL)[a]	568.85 (278.30; 1100.00)
MR-proANP[a] (pmol/L)	134.90 (94.44; 185.50)
sST2[a] (ng/mL)	28.92 (23.82; 35.02)
GDF-15	1231 (919; 1692)
Galectin 3	12.8 (10.6; 15.8)
hs-Troponin T[a] (ng/L)	13.75 (8.84; 21.90)
hs-Troponin I[a] (ng/L)	14.30 (9.40; 23.80)

[a] Median, 25th and 75th percentile.