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High-sensitive cardiac troponin T outperforms novel diagnostic biomarkers in patients with acute chest pain

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ABSTRACT

Background: Measurement of high-sensitive cardiac troponin (hs-cTn) has facilitated the early diagnostic assessment of chest pain patients. However, the information obtained from hs-cTnT levels might be improved when combined with results of other biomarkers of myocardial injury.
Methods: We measured admission levels of hs-cTnT (Roche Diagnostics), heart-type fatty-acid binding protein (H-FABP; Randox Laboratories) and copeptin using a novel ultra-sensitive (us) assay (Thermo Fisher Scientific) in 360 chest pain patients with a non-diagnostic ECG. Non-STEMI was defined according to the Universal Definition using cardiac troponin I (Stratus CS; Siemens Healthcare Diagnostics) as biochemical gold standard.
Results: Non-STEMI was diagnosed in 128 (36%) patients. Hs-cTnT had a greater diagnostic accuracy regarding non-STEMI (C-statistics 0.84) compared to H-FABP (C-statistics 0.80; $p = 0.04$) and us-copeptin C-statistics(0.62; $p < 0.001$). Compared to hs-cTnT alone, no increase in the C-statistics was noted for the combination of hs-cTnT with H-FABP (0.85; $p = 0.43$) or with us-copeptin (0.84; $p = 0.88$). Due to suboptimal sensitivities and/or specificities, neither H-FABP nor us-copeptin dichotomized at commonly applied diagnostic thresholds added information to hs-cTnT that would have facilitated early diagnostic assessment.
Conclusions: Hs-cTnT provides an excellent early diagnostic accuracy regarding non-STEMI already on admission. Neither H-FABP nor us-copeptin perform better or provide diagnostic increment to hs-cTnT levels.

1. Introduction

Patients with chest pain suggestive of a myocardial infarction represent up to 20% of all medical emergencies. Measurement of circulating levels of cardiac troponin (cTn) is a cornerstone in the diagnostic assessment of these patients [1,2]. However, the clinical utility of cTn has limitations as it takes some hours after an ischemic event until levels start to rise. Moreover, cTn may be elevated in other conditions than myocardial infarction but can also be negative in high-risk patients with unstable angina. Recent studies have consistently demonstrated that some of these problems might be overcome with the use of highly sensitive (hs) assays, allowing for the detection of myocardial infarction already in the first hours after onset of symptoms [3,4].

However, the diagnostic value of hs-cTn is not absolute. Consequently, there is an interest in biomarkers of myocardial necrosis and ischemia (by definition without cTn elevation) that could be used in conjunction to cTn results. Results from several recent studies have suggested that heart-type fatty acid-binding protein (H-FABP) and copeptin might be useful in this regard [3–7]. H-FABP is a small molecule that is abundant in the cytosol of cardiomyocytes and rapidly released into the circulation after myocardial injury [8]. Copeptin is the c-terminal part of the prohormone of arginine-vasopressin, known to rise compensatorily in clinical situations associated with hemodynamic stress [9] and now being measurable with a novel ultrasensitive (us) assay. The aim of this study was to investigate the utility of these novel biomarkers in addition to hs-cardiac troponin T (hs-cTnT) for the early diagnostic evaluation of patients with acute chest pain.

2. Methods

2.1. Study population

This analysis was performed in a pooled population of patients included in the FAST II- (Fast Assessment of Thoracic Pain) and FASTER I (Fast Assessment of Thoracic Pain by nEuRal networks)-studies

Abbreviations: cTn, Cardiac troponin; CI, Confidence interval; CV, Coefficient of variation; FAST, Fast Assessment of Thoracic Pain; FASTER, Fast Assessment of Thoracic Pain by nEuRal networks; H-FABP, Heart-type fatty-acid binding protein; Hs, Highly sensitive; non-STEMI, Non-ST segment elevation myocardial infarction; ROC, Receiver-operator characteristic; Us, Ultrasensitive.

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[10,11]. The primary aim of both studies was to assess the diagnostic utility of frequently measured cardiac troponin I (cTnI) levels in patients admitted to coronary care units because of acute chest pain and with a non-diagnostic ECG. The FAST II-study was conducted between May 2000 and March 2001 at the Uppsala University Hospital and enrolled 197 patients. The FASTER I-study was conducted between October 2002 and August 2003 at three teaching hospitals in Sweden and enrolled 364 patients. The inclusion criterion in both studies was chest pain with ≥15 min duration within the last 24 h (FAST II-study), or the last 8 h (FASTER I-study). Evidence of pathological ST-segment elevation on the admission 12-lead ECG leading to immediate reperfusion therapy or its consideration was used as exclusion criterion. All patients received standard therapy according to local routines.

Verbal and written informed consent was obtained from all patients, the study protocols had been approved by the hospitals independent ethics committees and complied with the declaration of Helsinki.

2.2. Definition of the index diagnosis

During the conduction of the FAST II- and FASTER I-studies, all index events were classified by independent endpoint-evaluators in accordance with the ESC/ACC consensus document and applying cTnI results determined with a contemporary assay (Stratus CS, Siemens Healthcare Diagnostics, Deerfield, IL, USA) as biochemical criterion [12]. cTnI had been measured serially at eight time points during the first 24 h following enrolment. Retrospectively, all admissions were re-classified according to the Universal Definition [1], applying the following biochemical criterion to define non-ST segment elevation myocardial infarction (non-STEMI): cTnI above the 99th percentile of 0.07 μg/L [13] at least at one measurement together with a ≥20% rise and/or fall and an absolute change ≥0.05 μg/L within 24 h. To allow for the calculation of relative changes, cTnI was set to 0.02 μg/L (i.e. a concentration below the lowest level of detection) when reported as 0.00 or 0.01 μg/L.

Patients with typical anginal pain at rest in combination with new or intercurrent ST-segment depression ≥0.05 mV or T-wave inversion in ≥2 contiguous leads but not fulfilling the biochemical criterion for non-STEMI were considered to suffer from unstable angina. Further diagnostic categories were other heart disease, non-cardiac disease and unspecified chest pain.

2.3. Biochemical analysis

Hs-cTnT was measured in plasma samples obtained at enrolment using an Elecsys 2010/cobas e 411 instrument (Roche Diagnostics, Mannheim, Germany). These samples had been stored frozen (−70 °C) since obtainment apart from one freeze-thaw cycle. The level of detection of the hs-cTnT assay is 3.0 ng/L, the 99th percentile among healthy subjects is 14.0 ng/L, and the lowest concentration measurable with a coefficient of variation (CV) <10% has been reported as 13.0 ng/L [14]. Hs-cTnT levels below the level of detection were assigned a value of 2.99 ng/L for the purpose of this analysis.

H-FABP was analyzed on the Evidence Investigator Cardiac Array using an immunoassay (Randox Laboratories Ltd., Antrim, UK) with a functional sensitivity (CV<20%) at 0.15 μg/L according to the manufacturer, and 5.8 μg/L as the 99th percentile among healthy subjects [15]. Copeptin was determined using the novel B·R·A·H·M·S us-copeptin immunoluminometric assay on the KRYPTOR Compact Plus system (Thermo Fisher Scientific, Hennigsdorf, Germany). This assay uses two polyclonal antibodies directed against the amino acid sequence 132–164 of the c-terminal region of arginine-vasopressin. Compared to its previous iteration [16], the us-assay utilizes Terbium as tracer substance and the handling temperature of the instrument has been improved. According to the manufacturer, the analytical range of the assay is 0.9 to 2000 pmol/L, the functional sensitivity is <2.0 pmol/L and the 95th percentile among healthy subjects is <12.0 pmol/L. The samples from which H-FABP and us-copeptin were determined had undergone 3-4 freeze-thaw cycles since obtainment.

2.4. Statistical analysis

Receiver-operating characteristic curve (ROC) analysis was performed to estimate the diagnostic accuracy of the assessed biomarkers with comparison of the C-statistics using the method described by DeLong [17]. In addition, the sensitivities, specificities, negative and positive predictive values with their 95% confidence intervals (CI) were calculated for each biomarker obtained from 1) commonly applied diagnostic thresholds (i.e. the 99th percentiles for hs-cTnT and H-FABP, and 14.0 pmol/L for us-copeptin [3,7,18], and 2) the concentrations providing a 95% specificity for non-STEMI according to ROC-analysis. Differences in sensitivities and specificities were assessed using the McNemar test.

Continuous variables are described as medians with 25th and 75th percentiles, if not stated otherwise. Comparisons of medians were performed with the Mann–Whitney *U* test. For the analysis of the correlations between continuous variables, Spearman rank-correlation coefficients were calculated. Categorical variables are expressed as frequencies and percentages with differences being analyzed with the χ^2 test. A two-tailed p value<0.05 was considered significant for all analyses. The software packages PASW 18.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 11.3.5 (MedCalc Software, Mariakerke, Belgium) were used.

3. Results

3.1. Baseline characteristics and index diagnoses

For this analysis, only patients from the FAST II- and FASTER I-studies with first-time admission and symptom onset <8 h before admission were considered (n = 495). Results for hs-cTnT, H-FABP and us-copeptin were available in 398, 443 and 367 of these patients respectively, which in part was due to a shortage of remaining samples. We therefore focused on the 360 patients with available results for all three biomarkers.

The median age of the sample population was 66.8 (25th, 75th percentiles 57.6–76.0) years and 65.6% were males. Non-STEMI was diagnosed in 128 (35.6%) patients, unstable angina in 68 (18.9%) patients, other cardiac disease in 29 (8.1%) patients, non-cardiac disease in 19 (5.3%) patients and 116 (32.2%) patients were considered to have unspecified chest pain. In total, 143 patients (39.7%) had a delay <4 h from onset of chest pain to blood sampling and of these, 49 had a non-STEMI. Further information on baseline characteristics is presented in Supplementary Table 1.

The median levels were 11.0 (2.99–36.7) ng/L for hs-cTnT, 2.2 (1.4–4.2) μg/L for H-FABP and 7.6 (4.2–20.0) pmol/L for us-copeptin. Neither the median levels of hs-cTnT, H-FABP nor us-copeptin differed with respect to onset of chest pain <4 or ≥4 h before blood sampling (data not shown). Hs-cTnT was strongly correlated to H-FABP (r = 0.74; p<0.001) and moderately to us-copeptin (r = 0.37; p<0.001). The correlation between H-FABP and us-copeptin was moderate (r = 0.48; p<0.001). Fig. 1A–C demonstrates that patients with non-STEMI had the highest median levels of all biomarkers. Compared to patients with unspecified chest pain, median hs-cTnT levels were significantly higher in any of the other diagnostic groups. Hs-cTnT >14.0 ng/L was observed in 101 (78.9%) patients with non-STEMI, 18 (26.5%) patients with unstable angina, 14 (48.3%) patients with other heart disease, 7 (36.8%) patients with non-cardiac disease and 20 (17.2%) patients with unspecified chest pain. Compared to patients with unspecified chest pain, median H-FABP levels were significantly higher only in patients with other