Clinica Chimica Acta 426 (2013) 18–24

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Head-to-head comparison of high-sensitivity troponin T and sensitive-contemporary troponin I regarding heart failure risk stratification

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ARTICLE INFO

Article history:
Received 13 June 2013
Received in revised form 25 July 2013
Accepted 15 August 2013
Available online 23 August 2013

Keywords:
Heart failure
Cardiac troponins
Prognosis
Survival

ABSTRACT

Background: High-sensitivity assays for cardiac troponins have recently become available, increasing the value of troponins in heart failure (HF) prognostication. We head-to-head compared the prognostic significance of high-sensitivity cardiac troponin T (hs-cTnT) and sensitive-contemporary cardiac troponin I (sc-cTnI) in an outpatient HF population.

Methods: We studied 876 patients, mainly of ischemic etiology (52.1%). Median left ventricular ejection fraction was 34%. Median follow-up was 3.45 years. Comprehensive statistical measurements of performance (discrimination, calibration, and reclassification) were obtained.

Results: hs-cTnT was ubiquitous in the patient cohort; sc-cTnI was detected in 276 patients (31.5%). During follow-up 311 patients died. According to multivariable Cox regression analysis, both hs-cTnT (HR 2.09, 95% CI 1.46–2.99, $P < 0.001$) and sc-cTnI (HR 1.61, 95% CI 1.24–2.08, $P < 0.001$) remained independent predictors of all cause and cardiovascular mortality. Using the best predictive cut-off point for both troponins calibration was better for hs-cTnT, which also reclassified a larger number of patients (NRI 9.0 [2.5;15.5] $P = 0.007$). The higher sensitivity of hs-cTnT permitted the identification of almost the double of deaths.

Conclusion: Both hs-cTnT and sc-cTnI predict mortality in a real-life cohort of ambulatory HF patients. However, hs-cTnT showed globally better measures of performance and identified a higher proportion of decedents during follow-up.

1. Introduction

Chronic HF is a real public epidemic [1]. Despite important progress in recent decades, mortality remains high for patients with HF. Risk stratification using clinical variables is often insufficient to estimate individual prognosis and requires the evaluation of circulating biomarkers to aid in clinical decision making.

Cardiac troponins, biomarkers of myocyte injury, are crucial in the diagnosis and prognosis of acute coronary syndromes and also predict adverse clinical outcomes in acute [2–4] and chronic HF [5,6]. High-sensitivity assays for cardiac troponin T and more efficient sensitive-contemporary assays for troponin I have become commercially available. These assays detect low troponin concentrations and improve precision at the lower limit of detection. Several clinical series have already suggested that both troponins provide useful prognostic information in different HF populations [7–15]. However, there has been limited head-to-head comparison of both assays in a long-term follow-up HF cohort. Accordingly, our aim was to compare the prognostic significance of commercially available sensitive troponin T and I assays in an outpatient HF population.

Abbreviations: hs-cTnT, high-sensitivity cardiac troponin T; sc-cTnI, sensitive-contemporary cardiac troponin I; HF, heart failure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AUC, area under the receiver-operating characteristic curve; AIC, Akaike information criterion; BIC, Bayesian information criterion; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NTproBNP, N-terminal pro-brain natriuretic peptide.

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http://dx.doi.org/10.1016/j.cca.2013.08.014

2. Material and methods

2.1. Study population

From May 2006 to July 2010, ambulatory patients treated at a multidisciplinary HF unit were consecutively included in the study. Patients were referred to the unit by cardiology or internal medicine departments, as well as (to a lesser extent) from the emergency or other hospital departments. The principal referral criterion was HF according to the European Society of Cardiology guidelines irrespective of etiology, at least one HF hospitalization, and/or reduced left ventricular ejection fraction (LVEF).

Blood samples were obtained by venipuncture between 9:00 a.m. and 12:00 p.m. during conventional ambulatory visits. After centrifugation, serum samples were stored at −80 °C; Both troponins were analyzed from the same blood sample.

All participants provided written informed consent and the local ethics committee approved the study. All study procedures were in accord with the ethical standards outlined in the Helsinki Declaration of 1975, as revised in 1983.

2.2. Follow-up and outcomes

All patients were followed at regular predefined intervals, with additional visits as required in cases of decompensation. The regular visitation schedule included a minimum of quarterly visits with nurses, biannual visits with physicians, and elective visits with geriatricians, psychiatrists, and rehabilitation physicians [15–17]. Patients who did not attend the regular visits were contacted by telephone.

Death from all causes was the main outcome. Fatal events were identified from HF unit clinical records or by reviewing the electronic clinical history at the Catalan Institute of Health, as well as by contacting the patients' relatives. Furthermore, data was verified from databases of the regional and national health systems.

2.3. sc-cTnI assay

Troponin I levels were measured using a sandwich chemiluminescence immunoassay based on LOCI® technology (Troponin I LOCI Siemens, RF621) and processed on the automatic analyzer Dimension® EXL™ Integrated Chemistry System (Siemens Diagnostics). As described by the manufacturer (RF 621, 2009-04-22 Siemens Healthcare Diagnostics Inc.), the 99th percentile for normal is 0–56 ng/L and the functional sensitivity (limit of quantification with coefficient of variation <10%) is 50 ng/L. The analytic measurement range for LOCI® Troponin I measured in Dimension® EXL™ is 17–40,000 ng/L without any dilution or pretreatment. In the insert this assay is considered as high-sensitivity based on imprecision and other performance characteristics, but in a recent population study [18] it is classified as sensitive-contemporary troponin I assay (sc-cTnI) and the 99th percentile for normal was found to be 34 ng/L (39 ng/L for men and 22 ng/L for women).

2.4. hs-cTnT assay

Troponin T levels were measured using an electrochemiluminescence immunoassay (ultra-sensitive troponin T method, ref 05092744 190 Roche Diagnostics) with a Modular Analytics E170 system (Roche Diagnostics). The analytic performance of this assay has been validated [19]. As described by the manufacturer (ref 05092744 190 Roche Diagnostics) the 99th percentile for normal is 14 ng/L and the functional sensitivity (limit of quantification with coefficient of variation <10%) is 13 ng/L. The cTnT assay analytic range is 3–10,000 ng/L. According to the recent population study [18] it is classified as high-sensitivity troponin T (hs-cTnT) assay and the 99th percentile for normal was found to be 15 ng/L (20 ng/L for men and 13 ng/L for women). The assays were run with reagents from lot 157123, not affected by the analytical issues emerged with Roche hs-cTnT assays.

Both methods demonstrate analytic performance in accordance with the recommendations of the Task Force for use in the diagnosis of myocardial necrosis [20].

2.5. Statistical analysis

Categorical variables were expressed as percentages. Continuous variables were expressed as the mean (standard deviation) or median (25th–75th percentiles, $P_{25–75}$) according to normal or non-normal distribution. Statistical differences between groups were compared using the chi-squared test for categorical variables. Correlation between the levels of sc-cTnI and hs-cTnT was analyzed using Spearman's rho.

Survival analyses were performed using Cox regression models. Density plots of the best cut-off point in non-adjusted Cox models were calculated using bootstrap methodology to identify the optimal prognostic cut-off points for both troponins.

The following variables were incorporated into the model: age, sex, LVEF (in percent), estimated glomerular filtration rate (eGFR calculated with the CKD-EPI equation after standardization of creatinine values according to IDMS reference method, in mL/min/1.73 m^2), New York Heart Association functional class, presence of diabetes mellitus, ischemic etiology, hemoglobin (g/dL), serum sodium (mmol/L), N-terminal pro-brain natriuretic peptide (NTproBNP) (ng/L), β-blocker treatment, and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) treatment. Log-rank tests for Kaplan–Meier survival curves were performed using the best cut-off points.

We used different measurements of performance to test the potential prognostic value of sc-cTnI and hs-cTnT (both as dichotomous variables; sc-cTnI distribution impeded its analysis as continuous variable), as follows:

a) *Discrimination*: The area under the receiver operating characteristic curve (AUC) summarized the diagnostic discrimination. Discrimination refers to a model's ability to correctly distinguish between two classes of outcomes. We used the index of rank correlation, Somers' D, which already incorporates information about censored data. To compare AUCs we used the method described by Pencina and D'Agostino [21].
b) *Calibration*: 1) The D'Agostino–Nam version of the Hosmer–Lemeshow calibration test was used to calculate a chi-squared value. A model is well calibrated when predicted and observed values agree for any reasonable grouping of the observation (no statistically significant differences in the Hosmer–Lemeshow test). 2) The Bayesian information criterion (BIC), the Akaike information criterion (AIC), and the Brier score were calculated for each model. The AIC and BIC are measures of the relative goodness of fit of a statistical model. The BIC penalizes free parameters more strongly than does the AIC. Brier score measures the average squared deviation between predicted probabilities for a set of events and their outcomes, so a lower score represents higher accuracy. It takes values between 0 and 1. Given any two estimated models, the model with the lower BIC, AIC, and Brier scores was preferred. No statistical tests compare different BIC, AIC, or Brier estimations, and lower values indicate a better model. 3) The global goodness-of-fit of the models was evaluated by likelihood ratio tests. A significant *P*-value in this test means that adding a new variable to the model significantly improves the model's accuracy.
c) *Reclassification*: We used the method described by Pencina et al. [22]. There are two main statistics to assess reclassification. The integrated discrimination improvement (IDI) considers the changes in the estimated mortality prediction probabilities as a continuous variable. $P < 0.05$ from two-sided tests was considered to indicate statistical significance. The net reclassification improvement (NRI) requires a previous definition of meaningful risk categories (we used tertiles