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The predictive potential of asymptomatic mild elevation of cardiac troponin I on mortality risk of stable patients with vascular disease ☆

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ABSTRACT

Objectives: Due to improved analytical performance of the newest generation of troponin assays, several patients have mild elevations of this parameter. Nevertheless, they do not show any signs of acute coronary syndrome. We speculated whether non-acute cardiac troponin I (cTnI) concentrations may improve prediction of residual mortality risk in clinically stable outpatients with chronic vascular disease.

Design and methods: We followed 830 patients (mean age 65.2 years) after myocardial infarction, coronary revascularization or first ischemic stroke (pooled Czech samples of EUROASPIRE III and EUROASPIRE-stroke surveys, interviewed in 2006/2007) in a prospective cohort study. In addition to standard protocol, troponin I and brain natriuretic peptide (BNP) was estimated from frozen samples. Vital status and declared cause of death from death certificates was registered to ascertain a 5-year all-cause and cardiovascular mortality.

Results: During a median follow up of 2050 days (5.6 years) 168 patients died. In the multivariate Cox proportional hazard model, cTnI ≥ 0.03 ng/mL independently predicted an all-cause 5-year mortality with HRR 1.76 (95% CI: 1.09–2.83). In the Cox model, the better predictor of mortality was BNP >150 ng/L [HRR 3.47 (95% CI: 2.23–5.41)]. However, the combination of BNP with cTnI did not substantially improve its sensitivity or predictive power.

Conclusion: We cannot confirm the utility of asymptomatic mild cTnI elevation as a tool to detect residual risk of stable patients with vascular disease. On the other hand, BNP seems to be more appropriate for this purpose.

Introduction

Patients in secondary prevention of vascular disease maintain a high mortality despite all therapeutic advances. Several biomarkers which reflect various underlying pathophysiological processes are currently studied to stratify the global risk of these patients beyond conventional models and to personalize therapeutic approach.

Cardiac troponins are accepted not only as the "gold standard" for diagnosis of myocardial ischemia and consequent necrosis [1]. Moreover, they provide important prognostic information in several clinical situations. The recently established "3rd Universal Definition of Myocardial Infarction" [2] predominantly lies on troponin values. For the diagnosis of myocardial infarction it is required "significant rise and/or fall in cardiac troponin above 99th percentile of healthy reference population" [2]. A number of new troponin show superior performance compared to older one. The new immunoassays enable us to detect the myocardial ischemia earlier, in the first few hours after development of acute coronary syndrome (ACS) [3], but also to quantify low-grade myocardial injury of various non-ACS etiologies. On the other hand, the improved sensitivity of these assays leads to a number of subjects with a mildly elevated troponin, which apparently does not have ACS or other hemodynamic condition, known to be associated with troponin elevation. It is uncertain, whether such mild elevation is of clinical importance and how to interpret it with regard to a potential residual risk. We investigated whether asymptomatic mild elevation of cardiac troponin I (cTnI) in clinically stable out-patients

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with chronic vascular disease represents any independent mortality risk.

Methods

Design and study population

The study represents a represents prospective cohort study in the setting of stable manifest vascular disease. The study population consists of Czech patients examined in the framework of two well-defined surveys in patients with coronary heart disease (CHD, EUROASPIRE III) [4] or in patients after first ischemic stroke (EUROASPIRE III-stroke survey) [5] in 2006/2007, the selection and standard protocol of examination were in details described elsewhere [4,5]. Both surveys were conducted in the two centers in the Czech Republic: the University Hospital Pilsen and the Cardio-Centre of Institute of Clinical and Experimental Medicine in Prague. The study was carried out according to the guidelines for Good Clinical Practice. Local Ethical Committees approved of the study protocols. All of the participants gave written informed consent. The data were stored and evaluated under the provisions of the Czech data protection act.

CHD patients (n = 600) [4] aged ≤80 years hospitalized for any of following discharge diagnosis were retrospectively identified from hospital records: first coronary bypass graft (CABG), first percutaneous trans-luminal coronary angioplasty (PTCA) and acute myocardial infarction or ischemia. Recruitment of patients started with the most recent hospital record and proceeded backwards until the required sample of 600 subjects was achieved. The stroke patients (n = 507) were selected in the same manner [5]. The hospital documentations of selected subjects were reviewed and all patients invited to attend the standard interview.

Clinical examinations and biochemical measurements

The interviews with patients were performed 6–36 months after the index event (coronary event or revascularization) in 832 responders, i.e. 491 (81.8%) CHD patients and 341 (67.3%) stroke patients. The standard protocol was followed, as described elsewhere [4,5].

Briefly, patients were interviewed at least 6 months after their index event. Information on personal and demographic characteristics, personal and family history of coronary heart disease, lifestyle and current pharmacotherapy were obtained. Following standardized examinations were performed: Height and weight were measured in light indoor clothes without shoes using SECA 220 scales and measuring sticks. Waist circumference was measured using steel tape measure. Blood pressure (BP) was measured twice in the sitting position on the right arm using standard mercury sphygmomanometer. Breath carbon monoxide was measured by SMOKERLYSER device (model EC 50, Bedfont Scientific, U.K.). Venous blood samples were drawn after at least 12 h of overnight fasting. All laboratory examinations were done in series from aliquots stored at −80°by the use of commercial kits and included: estimation of total (TCHOL), HDL cholesterol (HDL) and creatinine using ARCHITECT c800 analyzer (Abbott Laboratories, Germany) and DOT Diagnostics kits (Czech Republic), while triglycerides (TG), glucose (GLU) and brain-natriuretic peptide (BNP) using the same analyzer and Abbott standard kits. Troponin I (cTnI) was estimated using commercial AccuTnI kit on UniCel DxI 800 platform (Beckman-Coulter Inc., Brea, USA), with limit of detection 0.01 ng/mL. LDL cholesterol (LDL) was calculated by Friedewald equation i.e. LDL = TCHOL-HDL-(TG/2.22). Creatinine clearance was estimated by Cocroft–Gault formula, i.e. [(140-age) × body weight × (0.85 if female)/(72 × serum creatinine)].

Data management

Vital status of patients was registered up to May 31, 2012 using National mortality registry of Czech Institute for Medical Information and Statistics in Prague. Death certificates were used to specify the cause of death. From the present analysis, we excluded one CHD patient because of incomplete mortality data and one patient because of severe renal insufficiency.

Standard statistical analysis was done using STATISTICA 8, STATA/SE 8, and SAS 9.3 softwares, i.e. Mann–Whitney U and χ^2 test for unpaired comparison of cross-sectional variables. We used Spearman's correlation and multiple logistic regression to test the association between cTnI and BNP. We performed multivariate Cox proportional hazard regression (demonstrating hazard risk ratios and 95% confidence intervals, HRRs CI) to establish the predictive power of individual risk factors on 5-years all cause and cardiovascular mortality. We used Mantel–Cox log-rank test for comparison of survival curves. Moreover, we plotted receiver operating characteristic (ROC) curves and calculated the c-statistics. Conventional risk factors were dichotomized by usual cut-off points and specified in a relevant section of Results and Tables. For cTnI we initially used the manufacturer's recommended cut-off point >0.04 ng/mL. In the next step, we analyzed the data also using lower cut-off points: ≥0.03, ≥0.02 and ≥0.01 ng/mL (i.e. the lowest detectable concentration). For BNP we used the manufacturer's recommended (and clinically widely used) cut-off concentration >150 ng/L. For continuous analysis, the not-normally distributed parameters were logarithmically transformed.

Results

A total of 830 vascular patients, 489 with manifest coronary heart disease and 341 after first ischemic stroke were analyzed in the present study. The baseline characteristics of all patients and separate characteristics of those who survived or deceased during follow-up are given in Table 1. Patients who survived were significantly younger and more frequently had CHD. They had lower heart rate, LDL, BNP, cTnI, proportion of manifest heart failure and were less frequently treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. On the other hand, their diastolic blood pressure, creatinine clearance and proportion of antiplatelet treatment were higher compared to the deceased patients.

In total, 168 patients deceased during 2050 days (5.6 years) of follow-up, and of them, 126 due to cardiovascular disease. Corresponding 5-year all cause a cardiovascular mortality were 18.2% and 13.7%, respectively. The mortality rates in stroke patients were more than 2 times higher. Fig. 1 shows Kaplan–Meier survival curve. Patients with mild elevation of cTnI (>0.03 ng/mL) had significantly lower survival than those with lower cTnI values. We observed a “dose-dependent” relation between cTnI and mortality outcomes.

Table 2 shows potential predictors of all-cause and cardiovascular mortality in two different manners, excluding (*A*) and including (*B*) increased BNP. In both models, following independent variables significantly predicted the 5 year all-cause death: age, stroke as inclusion diagnosis, manifest heart failure, glycemia ≥ 7 mmol/L and cTnI ≥ 0.03 ng/mL. In model B BNP > 150 ng/L was significant and most powerful mortality predictor. Nearly similar results were observed using 5-year cardiovascular mortality as an dependent variable (with the exception of negative predictive power of obesity in model excluding BNP).

In contrast, when cut off value for cTnI > 0.04 was used, the significance of this parameter diminished after adjustment for increased BNP (i.e. model B) — *data not shown in Table section*. To further examine the effect of cTnI and BNP on mortality we calculated the C statistics (using continuous data). The C statistics for cTnI and BNP were 0.66 and 0.64, respectively.

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