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Diagnostic and prognostic value of a careful symptom evaluation and high sensitive troponin in patients with suspected stable angina pectoris without prior cardiovascular disease

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ABSTRACT

Background and aims: Typical angina pectoris (AP) and high-sensitive troponin I (hs-TnI) are independently associated with coronary artery disease (CAD) and future cardiovascular events (CVE). This study aimed to assess the individual and combined diagnostic and prognostic impact of symptoms and hs-TnI in stable chest pain patients without prior cardiovascular disease.

Methods: During a one-year period, 487 patients with suspected stable AP underwent invasive or CT-coronary angiography (significant stenosis ≥50%). At study inclusion, a careful symptom evaluation was obtained, and patients were classified as having typical AP, atypical AP, or non-cardiac chest pain. Hs-TnI was measured in all patients and divided into tertiles for analysis. Follow-up was a median of 4.9 years with cardiovascular death, non-fatal myocardial infarction, unstable AP, ischemic stroke, coronary-artery-bypass-grafting, percutaneous coronary intervention, and peripheral vascular surgery as combined endpoint.

Results: Hs-TnI was detected in 486 patients (99.8%). By multivariate regression analysis, typical AP and hs-TnI elevation were associated with increased risk of having significant CAD (typical AP, OR: 3.46; 95% CI: 2.07–5.79; $p < 0.0001$, hs-TnI, OR: 1.50; 95% CI: 1.12–2.01; $p = 0.007$) and experiencing future CVE (typical AP, HR: 2.64; 95% CI: 1.74–3.99; $p = 0.001$, hs-TnI, HR: 1.26; 95% CI: 1.06–1.49; $p = 0.008$). Patients in the lowest hs-TnI tertile, without typical AP (n = 107) had a 1.9% absolute risk of significant CAD and a 3.7% absolute risk of long-term CVE.

Conclusions: In clinical stable patients without known cardiovascular disease, a thorough chest-pain history in combination with hs-TnI testing can identify a significant low-risk group. The prognostic need for coronary angiography in these patients seems limited.

1. Introduction

Accurate risk estimation is important in the selection of appropriate diagnostic strategies. Recent European guidelines for the management of stable coronary artery disease (CAD) emphasize the importance of clinical assessment of the pre-test probability of CAD in risk estimation. The pre-test probability depends on a number of factors including age, gender, and the characteristic of chest pain/discomfort [1]. It has been reported that 62.4% of patients, who undergo elective invasive coronary angiography (ICA), and 76.5% who have coronary CT angiography (CCTA) performed, do not have significant CAD [2,3]. Thus, to improve risk stratification, a simple screening test, which can be used supplementary to clinical assessment, is still needed [1]. At present, ICA is considered the gold standard for diagnosing significant CAD. CCTA has a rather low positive predictive value, 64%, but the negative predictive value is excellent, 99–100% [4].

Release of cardiac troponins (cTn) into the blood circulation occurs with injury of cardiomyocytes. In patients with suspected acute coronary syndromes, cTn are the preferred biomarkers for diagnosis and risk stratification [5–7]. A recently developed high

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sensitive troponin I (hs-TnI) assay has enabled measurements of troponin in 89.3% of the general population [8]. In the general population, we also know that elevated hs-TnT predicts a greater risk of all-cause and cardiovascular mortality [9]. It has been suggested to consider hs-cTn as a risk factor alongside established risk factors like smoking, hypertension, and hyperlipidemia [10]. So far, hs-TnI has been shown to have prognostic impact in patients with stable CAD [11–13], and a diagnostic value in unclarified stable chest pain patients has also been reported [14–16]. In these stable patients, the characteristic of chest pain is closely related to CAD [17,18]. Furthermore, the presence of typical chest pain is associated with increased risk of cardiovascular events (CVE) in patients without significant CAD, in whom hs-TnI was not measured [19,20]. What remains to be investigated is if an association between chest pain symptoms and hs-TnI measurements – alone or in combination – and significant CAD or future CVE exists in clinical stable patients with suspected angina pectoris (AP), but without prior cardiovascular disease.

The purpose of the present study was, in a prospective design, to assess the clinical value of careful symptom evaluation and hs-TnI measurement individually and combined, in patients with stable chest pain but without known cardiovascular disease.

2. Materials and methods

2.1. Study population

The population of the present study has previously been described in detail [21]. During the one-year period from September 2010 to September 2011, clinical stable patients with suspected AP (n = 843), scheduled for either ICA or CCTA, depending on their pre-test probability of having CAD and the clinical judgement of the referring cardiologist, were prospectively enrolled. The large majority of patients came from our out-patient clinic. No patients with suspected acute coronary syndrome were included. To avoid potential confounding effects on the biomarkers measured, patients with established atherosclerotic manifestations, including an abnormal 12-lead rest electrocardiogram, were excluded: known ischemic heart disease (n = 138), prior ischemic stroke or transitory ischemic attack (n = 59), known peripheral artery disease (n = 10), and p-creatinine >200 mmol/L (n = 2). Informed consent could not be obtained for technical reasons in 42 patients. Furthermore, 89 persons did not wish to participate, and 10 were excluded because CCTA was not performed or was of poor technical quality. Five patients did not have hs-TnI measured, and one person had no history taken, leaving 487 for final inclusion: 336 for CCTA and 151 for ICA. Two independent, experienced cardiologists, who were blinded to the clinical and biochemical data, analyzed all angiograms.

Prospectively, we collected patient demographics, risk factors, medical history, and previous medical treatment.

2.2. Definitions

Significant CAD was defined as the presence of at least one coronary artery stenosis of 50% or more in at least one coronary artery on CCTA or ICA. The severity of AP was classified according to the Diamond Classification [22]. Thus, typical AP was defined as the presence of substernal chest pain or discomfort, with characteristic quality and duration, provoked by exertion or emotional stress and relieved by rest and/or nitrates. Atypical AP was defined as the presence of two criteria and non-cardiac chest pain was defined if only one of the criteria was present. Diabetes mellitus was defined if the patient took antidiabetic medication at the time of inclusion. Hypertension was defined as the use of antihypertensive medical treatment and/or a blood pressure ≥140/90 mmHg at the time of inclusion. Hypercholesterolemia was defined as the use of lipid-lowering medical treatment and/or a total cholesterol level ≥5 mmol/L, at the time of inclusion.

Clinical CVE included death caused by cardiovascular disease and the following diagnosis (ICD-10 codes): acute non-fatal myocardial infarction (MI) (DI21), unstable AP (DI200-DI200C), ischemic stroke (DI630-DI639), percutaneous coronary intervention (PCI) (KFNG), coronary artery bypass grafting (CABG) (KFNA-KFNE), and peripheral vascular surgery (KPEE-KPFQ).

2.3. Ethics

The study was performed in accordance with the Declaration of Helsinki, approved by the local ethics committee (S-20150179), and written consent was obtained from all patients. Follow-up data were obtained from the Danish Patient Register in which all discharge diagnoses for all hospital stays and all surgical procedures are registered.

2.4. Biochemical analyses

Blood samples were collected on the day of study inclusion during 2010 and 2011. All blood samples were drawn in tubes with EDTA and centrifuged at 200*g* for 10 min. Plasma and serum were stored at −80 °C until biochemical analysis (21). In spring 2012, we had access to the ARCHITECT STAT High Sensitive Troponin-I immunoassay on an ARCHITECT i2000SR immunoassay analyser (Abbott Diagnostics, USA), and samples (plasma) were analyzed with this analyser. The limit of detection was 1.9 ng/L. The assay supported a 10% coefficient of variation at a concentration of 4.7 ng/L and a 4% coefficient of variation at 26.2 ng/L.

2.5. Statistical analyses

Descriptive statistics were done according to data type. Continuous normally distributed variables are presented as the mean ± standard deviation, non-normally distributed variables as median and interquartile range (25^{th} and 75^{th} percentiles). The normality assumption was investigated visually by approximating normal distributions in histograms. Categorical variables are shown as frequencies and respective percentages (%). When hs-TnI was used as continuous variable, we applied base-2 logarithm-transforming due to right-skewness of the distribution. For some analyses, we divided the patients into tertiles of hs-TnI levels. To investigate any differences among tertiles, and among the three symptom groups, we used one-way analysis of variance (ANOVA) for normally distributed continuous variables and the non-parametric alternative, i.e. Kruskal-Wallis test, in case of non-normally distributed data. To compare differences among patients with and without typical AP and between atypical AP and non-cardiac chest pain, *t*-test and Wilcoxon rank sum test were used in normally and non-normally distributed data, respectively. Pearson Chi squared test or Fisher's exact test were used for categorical variables.

Logistic regression analyses were carried out to explain significant CAD by typical AP and hs-TnI, while Cox regression analyses were performed to investigate the risk of CVE with typical AP/hs-TnI as explanatory factors. For graphical representation, cumulative incidence curves were created for event-free survival in patients with and without typical AP, and by tertiles of hs-TnI level, and groups were compared using the log-rank test.

To decide which clinical risk factors to include in the multivariate analysis, univariate regressions were applied on all variables potentially explanatory on CAD (age, gender, smoking, diabetes,

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