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Association between high-sensitive troponin I and coronary artery calcification in a Danish general population

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ABSTRACT

Background: High-sensitive troponin I (hs-TnI) is an individual predictor of future cardiovascular disease (CVD). However, the relationship between hs-TnI and coronary artery calcification (CAC) as determined by computed tomography (CT) has not previously been investigated in a general population.
Methods: 1173 randomized, middle-aged subjects without known CVD underwent a non-contrast cardiac-CT scan for CAC determination. Hs-TnI was detected using ARCHITECT STAT High Sensitive Troponin-I immunoassay. Total 10-year cardiovascular mortality risk was estimated using HeartScore. The relationship between hs-TnI and CAC was assessed using logistic regression analyses and receiver operating characteristic curves (ROC).
Results: Concentrations of hs-TnI above the limit of detection were measured in 89.3% of all subjects. Presence of CAC (Agatston score >0) was detected in 29% in the lowest hs-TnI quartile compared with 55% in the highest, with a stepwise increase over the quartiles. In fully adjusted regression models with dichotomous CAC outcomes, hs-TnI was able to predict presence of CAC (OR: 1.25, 95% CI: 1.03–1.51, $p = 0.025$) and an Agatston score >100 (OR: 1.36, 95% CI: 1.08–1.71, $p = 0.009$). Subjects in the fourth hs-TnI quartile had an increased risk for presence of CAC (OR: 1.56, 95% CI: 1.06–2.26, $p = 0.024$) and for an Agatston score >100 (OR: 1.82, 95% CI: 1.04–3.18, $p = 0.035$), when compared with the first quartile. Addition of hs-TnI to HeartScore improved the ROC_{AUC} from 0.671 to 0.695 ($p < 0.0001$).
Conclusion: Hs-TnI was associated with CAC in a Danish middle-aged population without previously known CVD. This is a step towards understanding hs-TnI as a risk marker for CVD.

1. Introduction

Cardiovascular disease (CVD) is the most frequent cause of death world-wide [1]. The development of acute myocardial infarction (AMI) is most often precipitated by acute rupture of a coronary plaque that has been asymptomatic for years. For primary prevention, it is highly relevant to find a screening method able to recognize subjects with increased risk for CVD in the asymptomatic phase of the disease. The currently used clinical tools for estimation of cardiovascular risk are score charts, based on traditional cardiovascular risk factors, such as the European HeartScore [2] which is implemented in the European guidelines on prevention of CVD. These risk scores are derived from studies on large populations and lack an individualized risk assessment. Subclinical coronary artery disease, as determined by computed tomography (CT) imaging for the detection of coronary artery calcification (CAC) has been shown to add prognostic information independent of traditional risk factor scores [3–5]. CT-imaging, however, is expensive, exposes the patient to radiation and is hard-to-implement in primary preventive

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medicine. Recent research has focused on a more cost-effective and easy-accessible risk prediction marker with the ability to predict future CVD.

The development of new high-sensitive assays for cardiac troponins (cTn) has made it possible to detect low concentrations in the general population [6], and a recent large study addressing the long term follow-up of a general population without symptomatic CVD has shown that high-sensitive troponin I (hs-TnI) is an independent predictor of cardiovascular events and coronary death [7].

The cause of elevated cTn in a healthy population is still not fully understood. One possible explanation, strengthened by the research of Koroglosou et al. [8], states that repetitive microruptures of atherosclerotic plaques cause embolization of the coronary microcirculation and a subsequent leak of hs-TnI, which is detectable with the new high-sensitive assays and therefore should reflect an increased atherosclerotic burden.

The purpose of the present study was twofold: To examine the distribution of hs-TnI in a middle-aged, Danish general population without known CVD, and to investigate if hs-TnI is associated with CAC.

2. Materials and methods

The study design and population has previously been described in detail in the original DanRisk study [9]. In 2009, a total of 1825 men and women from the Region of Southern Denmark, 50 or 60 years old, were randomly selected from the Danish national population register and invited to participate in the observational DanRisk study. 1257 accepted the invitation and were asked to fill out a questionnaire concerning current and previous medical conditions, current medication, smoking habits and family history of CVD. The questionnaire was supplemented by a thorough medical history, a clinical examination, and a cardiac CT-scan performed at one of four regional hospitals in Southern Denmark (Odense, Vejle, Esbjerg, or Svendborg). The examination consisted of measurements of weight, height, and waist circumference. Body mass index (BMI) was calculated. After 5 min of supine rest, blood pressure was recorded three times. The last two values were averaged for the analyses. Blood samples were collected and a biobank was established. Laboratory tests were performed to determine blood glucose and lipid levels. If the capillary blood glucose was $\geq$6.1 mmol/L, fasting plasma blood glucose was measured.

For the present study, a total of 84 of the 1257 subjects were excluded due to known CVD in the medical history (n = 42; 15 with angina or previous MI, 14 with stroke, 10 with atrial fibrillation, 2 with peripheral artery disease and 1 with valvular heart disease) or due to missing blood samples (n = 42), ending up with a total of 1173 subjects.

The protocol was approved by the Central Ethical Committee and was conducted in accordance with. The Declaration of Helsinki. Written informed consent was obtained from each participant.

2.1. Definitions

Diabetes mellitus was defined as the use of antidiabetic medication, fasting plasma blood glucose level $\geq$7.0 mmol/L on two different days and/or a postprandial blood glucose level $\geq$11.1 mmol/L. Hypertension was defined as the use of antihypertensive medical treatment and/or a blood pressure $\geq$140/90 mmHg at the time of examination. Hypercholesterolemia was defined as the use of lipid-lowering medical treatment, a total cholesterol level $\geq$5 mmol/L and/or a LDL cholesterol level $\geq$3 mmol/L. The 10-year cardiovascular mortality risk was calculated based on age, gender, smoking status, blood pressure and total cholesterol, according to the HeartScore risk chart [2]. HeartScore was categorized using following limits: low risk <1%, moderate risk 1–5%, high risk 5–10%, very high risk >10%. Presence of CAC was defined as an Agatston score >0.

2.2. Coronary artery calcification

In all four centers the scan data was acquired during an inspiratory breath hold. Experienced cardiologists calculated the Agatston score [10] by summing up the scores from each of the foci found in the coronary arteries. 64-slice CT-scans were obtained with the following technical setup: two of the centers (Odense, Svendborg) used a GE 64-slice CT-scanner (Discovery VCT; GE Healthcare) with gantry rotation time 500 ms, 16 × 2.5 mm collimation, 120 kV tube voltage, 200 mA tube current and a prospectively ECG-triggered scan acquisition gating at 50% of the R–R interval. The third center (Vejle) used a Siemens 64-slice Dual Source CT-scanner (Siemens Definition; Siemens Medical Solutions) with gantry rotation time 330 ms, 3.0 mm collimation, 100–120 kV tube voltage, 150 mA tube current and a prospectively gating at 60% of the R–R interval. The fourth center (Esbjerg) used a Toshiba 64-slice CT-scanner (Aquilion; Toshiba Medical Systems) with gantry rotation time 450 ms, 3.0 mm collimation, 120 kV tube voltage and a prospectively gating at 75% of the R–R interval. The interobserver variability of the Agatston score was assessed by a blinded reanalysis of 10% of the CT-scans. The agreement rate with regard to presence of calcification was 90%, κ value 0.81 (95% CI 0.71–0.91) [9].

2.3. Biochemical analyses

Hs-TnI concentrations were measured in EDTA-plasma samples, which had been stored at −80 °C until analysis. The samples were analyzed using the ARCHITECT STAT High Sensitive Troponin-I immunoassay on an ARCHITECT i2000SR immunoassay analyzer (Abbott Diagnostics, USA). The Limit of Detection (LoD) for the assay was 1.9 ng/L, observed values below the LoD were included in subsequent analyses (assay range 0–50 000 ng/L). The assay supported a 10% coefficient of variation (CV) at a concentration of 4.7 ng/L and a 4% CV at 26.2 ng/L.

2.4. Statistical methods

Baseline characteristics are expressed as absolute values and percentages for categorical variables, means and SD for normally distributed continuous variables and medians and quartiles for non-normally distributed continuous variables. Normal distribution was determined on the basis of empirical histograms. Due to right-skewness, hs-TnI was transformed to its natural logarithm. For some analyses, hs-TnI was categorized using quartiles. CAC measured by Agatston score was categorized into four levels using well-established limits: 0, 1–99, 100–399 and $\geq$ 400. For subanalyses, age and sex-specific quartiles of hs-TnI were calculated and used to display differences. Differences in hs-TnI and CAC between men and women were assessed using Wilcoxon rank-sum test.

The relationship between hs-TnI and CAC as continuous variables was calculated using Spearman's rank correlation coefficient. A non-parametric trend test across ordered groups was used to test for a trend of increasing CAC across hs-TnI quartiles [11].

The association between CAC and hs-TnI was assessed by logistic regression analyses. Both univariate and multivariate logistic regressions were used with hs-TnI as continuous variable as well as categorized by quartiles. Regressions were performed separately with three different dichotomous CAC outcomes (Agatston score