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The mediation of coronary calcification in the association between risk scores and cardiac troponin T elevation in healthy adults: Is atherosclerosis a good prognostic precursor of coronary disease?

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ABSTRACT

Background. Conventional cardiac risk scores may not be completely accurate in predicting acute events because they only include factors associated with atherosclerosis, considered as the fundamental precursor of cardiovascular disease. In UK in 2006–2008 (Whitehall II study) we tested the ability of several risk scores to identify individuals with cardiac cell damage and assessed to what extent their estimates were mediated by the presence of atherosclerosis.

Methods. 430 disease-free, low-risk participants were tested for high-sensitivity cardiac troponin-T (HS-CTnT) and for coronary calcification using electron-beam, dual-source, computed tomography (CAC). We analysed the data cross-sectionally using ROC curves and mediation tests.

Results. When the risk scores were ranked according to the magnitude of ROC areas for HS-CTnT prediction, a score based only on age and gender came first (ROC area = 0.79), followed by Q-Risk2 (0.76), Framingham (0.70), Joint-British-Societies (0.69) and Assign (0.68). However, when the scores were ranked according to the extent of mediation by CAC (proportion of association mediated), their order was essentially reversed (age&gender = 6.8%, Q-Risk2 = 9.7%, Framingham = 16.9%, JBS = 17.8%, Assign = 17.7%). Therefore, the more accurate a score is in predicting detectable HS-CTnT, the less it is mediated by CAC; i.e. the more able a score is in capturing atherosclerosis the less it is able to predict cardiac damage. The P for trend was 0.009.

Conclusions. The dynamics through which cardiac cell damage is caused cannot be explained by 'classic' heart disease risk factors alone. Further research is needed to identify precursors of heart disease other than atherosclerosis.

Background

The pathophysiology of heart disease has been studied for centuries (Nabel & Braunwald, 2012) and our knowledge of the disease has undergone a remarkable evolution during the past decade (Libby, 2013). Coronary atherosclerosis, indicated as the fundamental precursor of coronary artery disease, was previously considered as a passive cholesterol storage disease whereas we currently view it as an inflammatory disorder and modern views of the dynamics underlying acute cardiac events also highlight the role of inflammation. Therefore our understanding of phenomena such as lesion formation, arterial remodelling, plaque rupture, thrombosis, and others will likely continue to evolve (Libby, 2013).

Risk assessment is an important part of routine clinical practice, and tools for the prediction of coronary artery disease (CAD) events in healthy subjects and the correlated administration of preventive cures have a long history (About the Framingham Heart Study). However, in spite of our constant progress in the comprehension of CAD pathophysiology, standard risk algorithms are based on the idea that cardiac events arise through the accumulation of coronary atherosclerosis and widely-used tools like the Framingham, the Joint British Societies & British National Formulary, the Assign, and the Q-Risk scores are still based on variables such as age, gender, blood lipids, blood pressure, and other 'classic' risk factors associated with atherosclerosis, as it was traditionally conceived (D'Agostino et al., 2008; British Cardiac Society et al., 2005; Woodward et al., 2007; Hippisley-Cox et al., 2008). The standard risk algorithms may not therefore be completely accurate in predicting cardiac events, rather than coronary stenosis, because they only include factors associated with 'passive' atherosclerosis, considered as the main mediator for CAD events.

Cardiac Troponin T (CTnT) is a plasma protein routinely tested for the diagnosis of acute myocardial infarction (AMI), since it is a marker of myocardial cell damage (Thygesen et al., 2007). In clinical settings,

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CTnT is measured using standard assays that have a lower detection limit of 10 ng/L (Wallace et al., 2006) and a diagnostic threshold of 35 ng/L (Thygesen et al., 2007; Wallace et al., 2006). However, high-sensitivity assays have recently been developed (HS-CTnT) with a lower detection limit of 3 ng/L (Giannitsis et al., 2010; Collinson, 2011; Collinson et al., 2012). In healthy people not fulfilling any diagnostic criterion for AMI, greater HS-CTnT is associated with greater incidence of AMI, other structural and functional heart diseases, cardiovascular mortality, and all-cause mortality, and can be therefore considered the most proximal sentinel marker of heart disease (De Lemos et al., 2010; deFilippi et al., 2010).

The mechanisms and clinical relevance of HS-CTnT in apparently low risk participants remains poorly understood, and further research is needed to understand if HS-CTnT should be included in screening tools as part of routine clinical practice. However, identifying groups of people with low risk profile, absent coronary calcification, but with detectable HS-CTnT would create a momentum towards the exploration of new pathophysiologic dynamics of heart disease.

The aim of this study was to test the ability of the Framingham, the Joint British Societies & British National Formulary (JBS/BNF), the Assign, and the Q-Risk 2 scores to identify individuals with detectable HS-CTnT plasma concentration in people with and without apparent atherosclerosis as defined by coronary artery calcification (CAC) and to assess to what extent their estimates are mediated by CAC.

Methods

Study design

Our cross-sectional study involved participants drawn from the Whitehall II epidemiological cohort (Marmot et al., 1991) between 2006 and 2008 in United Kingdom. The criteria for entry into the study included no history or objective signs of clinical or subclinical CVD, no previous diagnosis or treatment for hypertension, inflammatory diseases, allergies, or kidney disease. CVD was defined as prior myocardial infarction, stable or unstable angina, revascularization procedure, heart failure, transitory ischaemic attack, stroke, or electrocardiographic abnormalities (resting 12-lead electrocardiograms were taken). This information was confirmed by a telephone interview and verified from clinical data collected from the previous seven phases of the Whitehall II study. Volunteers were of white European origin, aged 53–76 years, and 56.5% were in full-time employment. Selection was stratified by grade of employment (current or most recent) to include higher and lower socioeconomic status participants. From the initially invited participants (n = 1169), 27.6% were not eligible (mainly because of prescribed medications) and 25.9% declined to take part. Participants were prohibited from using any medication from seven days before testing and were rescheduled if they reported colds or other infections on the day of testing. Participants gave full informed consent to participate in the study and ethical approval was obtained from the UCLH committee on the Ethics of Human Research. The study conformed to the principles of the declaration of Helsinki.

Data collection

Non-fasting blood samples were collected in EDTA tubes and centrifuged immediately at 2500 rpm for 10 min at room temperature. Plasma was removed from the tube and aliquoted into 0.5 ml portions and stored at 80 °C until analysis. We measured cardiac troponin T concentrations using a highly sensitive assay on an automated platform (Elecsys-2010 Troponin T hs STAT, Roche Diagnostics), with a lower detection limit of 3 ng/L and a reported 99th percentile value in apparently healthy individuals of 13.5 ng/L, at which the CV is 9%, confirmed by in house studies (Giannitsis et al., 2010; Collinson, 2011; Collinson et al., 2012).

The assessment of coronary artery calcification (CAC) was performed using electron beam computed tomography (GE Imatron C-150, San Francisco, CA, USA) as previously described (Anand et al., 2007). In brief, 40 contiguous 3 mm slices were obtained during a single breath-hold starting at the carina and proceeding to the level of the diaphragm. Scan time was 100 ms/slice, synchronized to 40% of the R-R interval. Agatston and volumetric calcium scores were calculated to quantify the extent of CAC by a single experienced investigator blinded to the psychophysiological and clinical data on an Aquarius workstation (TeraRecon Inc., San Mateo, CA, USA). Since calcified volume was very highly correlated with Agatston score (Spearman's rho = 0.99), we present data for Agatston score only.

Participants reported current smoking levels. We measured height and weight in light clothing for the calculation of body mass index (BMI). Fasting blood samples were taken during a separate clinical assessment. Total and high-density lipoprotein (HDL) cholesterol and triglycerides were measured within 72 h in serum stored at 4 °C using enzymatic colorimetric methods (Brunner et al., 1997). Low-density lipoprotein (LDL) cholesterol was derived using the Friedewald equation (Warnick et al., 1990). Glucose homeostasis was assessed from glycated haemoglobin (HbA1C) concentration, assayed using boronate affinity chromatography, a combination of boronate affinity and liquid chromatography.

Data analysis

Data analysis was performed using Stata v.13. We checked the dataset for missing and inconsistent values, as well as normality, outliers, and digit preference for linear variables. We excluded 83/543 people (15.3%) with prescribed statins or diabetes. Out of the remaining 460 participants, 30 (6.5%) had missing information for HS-CTnT due to insufficient blood samples, and the final analytic sample therefore comprised 430 people. HS-CTnT was highly right-skewed and for 83.3% (n = 358) of the sample it was undetectable (below the lower detection limit of 3 ng/L) and so it was transformed into a binary variable (detectable vs undetectable). We calculated the Framingham (general CVD, primary model), the JBS/BNF, the Assign, and the Q-Risk2 scores for the risk of CVD events within ten years using information about age, gender, total cholesterol, HDL, systolic blood pressure, smoking, diabetes, history of CVD (not for Assign), family history of CVD (not for Framingham and JBS/BNF), BMI (Q-Risk2 only), ethnicity (Q-Risk2 only), and rheumatoid arthritis (Q-Risk2 only) (D'Agostino et al., 2008; British Cardiac Society et al., 2005; Woodward et al., 2007; Hippisley-Cox et al., 2008). The computation of the Assign and the Q-Risk2 algorithms includes optional variables consisting of area-based socio-economic deprivation scores for UK, and we opted to use their default values (20 for Assign and zero for Q-Risk2) so that the predictions were based on clinical variables only and were therefore comparable to the ones from the other algorithms, which do not consider such variables. We also calculated a simple risk score based on age and gender only. To do this we fitted a logistic regression model with age and gender as covariates and HS-CTnT as outcome and calculated the predicted probability of HS-CTnT prevalence (Cleves, 2002).

We performed non-parametric ROC analysis to assess the accuracy of each risk score in predicting the presence of detectable HS-CTnT and compared each of these estimates with the one based on age and gender alone (reference).

We used binary mediation analysis to assess to what extent the association between each risk score and HS-CTnT was mediated by CAC (Stata FAQ). In particular, we calculated the proportion of the effect that is mediated (Stata FAQ) and its 95% confidence intervals using bootstrapping (1000 replications) (Mooney, 1993). Similarly to the ROC analysis, we used the score based on age and gender as the referent equation for the comparisons.

We performed a statistical test for trend using the following strategy: we constructed a 5 × 2 table containing the results from the ROC analysis and from the mediation analysis for each score and calculated a P for trend using linear regression.

Sensitivity analyses

We considered CAC in several different ways: linear; log-linear; binary with a cut-off at zero; binary with a cut-off at 100 (this threshold was based on the St Francis Heart Study that demonstrated maximum sensitivity and specificity for detecting cardiovascular events at a threshold calcium score ≥ 100 (Arad et al., 2005)); and ordered categorical with cut-offs at 0, 100, and 400. The score based on age and gender was calculated including an interaction term between age and gender (multiplicative model) since risk algorithms are usually gender specific. A second score based on age and gender was calculated including measures of systemic inflammation (Interleukin-6 and C-reactive protein) since they are considered as novel risk factors for CVD. Instead of fitting the ROC models using the risk scores directly, we used the same procedure as for age and gender, i.e. we first fitted a logistic regression model using the risk score as exposure and HT-CTnT as outcome, we then calculated the predicted probabilities, and then used those to fit the ROC model (Cleves, 2002). We used linear (Stata FAQ) instead of binary mediation.