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Gender and age effects on risk factor-based prediction of coronary artery calcium in symptomatic patients: A Euro-CCAD study

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ABSTRACT

Background and aims: The influence of gender and age on risk factor prediction of coronary artery calcification (CAC) in symptomatic patients is unclear.
Methods: From the European Calcific Coronary Artery Disease (EURO-CCAD) cohort, we retrospectively investigated 6309 symptomatic patients, 62% male, from Denmark, France, Germany, Italy, Spain and USA. All of them underwent risk factor assessment and CT scanning for CAC scoring.
Results: The prevalence of CAC among females was lower than among males in all age groups. Using multivariate logistic regression, age, dyslipidaemia, hypertension, diabetes and smoking were independently predictive of CAC presence in both genders. In addition to a progressive increase in CAC with age, the most important predictors of CAC presence were dyslipidaemia and diabetes ($\beta = 0.64$ and 0.63, respectively) in males and diabetes ($\beta = 1.08$) followed by smoking ($\beta = 0.68$) in females; these same risk factors were also important in predicting increasing CAC scores. There was no difference in the predictive ability of diabetes, hypertension and dyslipidaemia in either gender for CAC presence in patients aged <50 and 50–70 years. However, in patients aged >70, only dyslipidaemia predicted CAC presence in males and only smoking and diabetes were predictive in females.
Conclusions: In symptomatic patients, there are significant differences in the ability of conventional risk factors to predict CAC presence between genders and between patients aged <70 and ≥70, indicating the important role of age in predicting CAC presence.

1. Introduction

Coronary artery calcification (CAC) is calcium formation in one or more of the layers of the coronary wall. It is an independent predictor of cardiovascular (CV) events and all-cause mortality in both CV and renal patients [1,2] and is thought to be a manifestation of sub-clinical atherosclerosis in asymptomatic individuals [3]. Significant CAC can cause diffuse hardening of the arteries, which may result in exertional angina even in the absence of significant flow limiting lesions [4]. Since treatment of atherosclerosis by statins fails to attenuate CAC progression [5], it might be helpful to determine the potential relationship of CAC with other conventional CV risk factors, with the hope that their treatment might reduce CAC formation.

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The conventional CV risk factors (dyslipidaemia, hypertension, diabetes mellitus, family history of coronary artery disease (CAD), obesity and smoking) have proved useful in quantifying the estimated 10-year coronary event risk [6] but their relationship with CAC presence has not been fully determined in symptomatic patients. The European Calcific Coronary Artery Disease (EURO-CCAD) study, an international platform established in 2009 in Umeå, Sweden, was initiated with the objective of increasing knowledge of the relationship between coronary calcium and conventional as well as other risk factors. This retrospective cross-sectional study investigates the influence of gender and age on the relationship between conventional CV risk factors and CAC presence in 6309 symptomatic patients.

2. Patients and methods

Retrospective data were collected from seven heart centres in six countries, on symptomatic patients with intermediate (10–20%) 10-year risk for developing coronary heart disease [7]. Some data were collected from registries. Patients may have typical or atypical angina symptoms; data allowing classification of chest pain as typical angina, atypical angina or non-cardiac chest pain as defined by Diamond [8] were not available although it was estimated that the majority had typical angina. Patients received a thorough clinical examination and assessment of conventional risk factors for CAD, together with coronary calcium scoring using the local CT protocol.

These patients were collected from the following centres:

Denmark: 1015 patients from 2 centres
France: 547 patients
Germany: 351 patients
Italy: 3336 patients
Spain: 186 patients
USA: 874 patients.

The exclusion criteria for this study were:

- acute coronary syndrome or recent cardiovascular event
- stroke or transient ischaemic attack
- cardiac valve disease
- atrial fibrillation
- prior coronary intervention (percutaneous intervention or bypass graft surgery)
- heart failure or previous decompensation
- chronic kidney disease (creatinine >120 mmol/l)
- parathyroid disease
- pregnancy.

2.1. Computed tomography scanning protocol

CT scanning for coronary calcification was undertaken with the patient in the supine position. The heart was localized by low-dose, low-resolution spiral CT imaging of the chest. High-resolution scanning of the heart was begun at the level of the bifurcation of the main pulmonary artery and proceeded caudally through the cardiac apex. Rotation and slice acquisition protocols were adopted according to individual scanners and local protocols. At least four contiguous pixels with a CT density ≥130 Hounsfield units were used to define an area of CAC. The total CAC score (CACS) was computed from all calcified lesions by means of the Agatston score, calculated by multiplying the area of each lesion by a density factor and then summing the individual lesion scores [9]. Analyses were performed using local protocols and workstations [10].

2.2. Risk factor assessment

All centres used standard definitions for risk factors. Diabetes was defined as overnight fasting blood glucose ≥7 mmol/l (126 mg/dl), postprandial blood glucose ≥11 mmol/l (200 mg/dl) or use of insulin or oral hypoglycemic agents. Blood lipids were measured using standard enzymatic methods. Hypercholesterolaemia was defined as total cholesterol >5.0 mmol/l (193 mg/dl), low density lipoprotein cholesterol >3.00 mmol/l (116 mg/dl) or use of lipid-lowering medication. Body mass index (BMI) was calculated using height and weight measurements, with BMI ≥30 kg/m^2 indicating obesity. Family history of premature CAD was noted if a male first-degree relative developed CAD aged <55 years or a female first-degree relative aged <65 years. Hypertension was defined according to the JNC-7 guidelines as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg and/or use of antihypertensive medication [11]. Patient was classified as smokers if they had smoked during the last month. A total risk factors score was created by counting 1 for each risk factor present, with the exception of age.

2.3. Statistical analysis

Statistical analysis was undertaken using IBM SPSS Statistics version 22 (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as mean ± SD or median, and differences between groups were analysed by Student's *t*-test or Mann-Whitney test, as appropriate. Categorical variables were expressed as absolute value and percentage and differences were analysed by Chi-square test. Covariates-adjusted odds ratios (OR) and 95% confidence intervals (CI) of risk factors were derived from the Multivariate Logistic Regression models. To assess the stability of the derived models, 10-fold cross-validation was used, where the corresponding classification accuracy, sensitivity and specificity were determined for each of the ten models. Classification results based on different sets of explanatory variables were compared using nonparametric methods. A *p*-value of <0.05 was considered statistically significant. For obesity, approximately 40% of values were missing and consequently obesity was analysed separately. Patients with missing values were excluded from the Multivariate Logistic Regression analysis.

3. Results

3.1. Comparison of prevalence of risk factors between males and females, with and without CAC

Table 1 shows the distribution of risk factors according to gender in 6309 symptomatic patients classified by whether or not they had any CAC. This analysis shows that irrespective of the presence or absence of CAC, females recruited into this study were older than males by approximately 5 years. The mean age of males with CAC was 62 years, compared to those with zero CAC whose mean age was 51 years, whereas in females the mean age of those with CAC was 66 years, with a mean age of 57 years in those with zero CAC. Regardless of CAC presence, females more frequently had hypertension and a family history of CAD, whereas males were more frequently smokers and had a higher number of risk factors. In patients with zero CAC, females more frequently had dyslipidaemia. There was no difference between males and females for incidence of diabetes or obesity, irrespective of CAC presence, and in patients with CAC there was no difference in the incidence of dyslipidaemia between genders.

Table 2 shows the distribution of the proportion of males and females with and without CAC in different age groups. This shows