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Relationship between Syntax Score and prognostic localization of coronary artery lesions with conventional risk factors, plasma profile markers, and carotid atherosclerosis (CAPP Study 2)

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ABSTRACT

Background: Data concerning the relationship between cardiovascular risk factors, plasmatic markers, carotid disease and extent of coronary lesions are lacking.
Objectives: To evaluate the role of cardiovascular risk factors, plasmatic levels of high sensitivity C-reactive protein (hs-CRP), fibrinogen, lipoprotein(a), and carotid plaque extension in predicting the severity of coronary artery disease (CAD).
Methods: We analyzed 574 subjects undergoing first coronary angiography. For angiographic analysis, we used the Syntax Score and we defined the prognostic localization of CAD as a critical stenosis of the left main and/or proximal segment of left anterior descending artery. Levels of hs-CRP >3 mg/L, lipoprotein(a) plasma levels >30 mg/dL and plasma fibrinogen >300 mg/dL were considered critical. Significant carotid disease (SCD) was defined by the presence of lesions producing a 50% diameter stenosis with a peak systolic velocity >125 cm/s. A mean carotid intima media thickness (IMT) >0.9 mm was considered abnormal.
Results: In the adjusted analysis the presence of SCD was found to be an independent predictor of high Syntax Score ($p < 0.001$), while high fibrinogen levels were independently associated with the presence of CAD in prognostic localization ($p = 0.04$). In the sub-group of patients without SCD, IMT >0.9 mm was found to be an independent predictor of the presence of CAD ($p < 0.001$).
Conclusions: SCD strongly predicts high Syntax Score, while IMT shows excellent positive predictive value for the presence of CAD. In addition, high plasma fibrinogen levels are associated with coronary stenoses in prognostic localization.

1. Introduction

Atherosclerosis is a diffuse progressive condition that usually affects at the same time coronary, cerebrovascular, and peripheral vascular territories.

Traditional risk factors are considered to be useful in predicting the localization of atherosclerosis [1] but their impact on severity and prognostic localization of coronary artery disease (CAD) is not well established.

In this setting, morbidity and mortality are generally related to the extent of coronary artery lesions and it is widely accepted that critical disease of the left main or the proximal left anterior descending is associated with an increased rate of cardiac mortality [2–5].

Multiple biomarkers, representing key biological pathways, have been associated with the extent of atherosclerosis [6,7], suggesting that its onset and progression likely represent the combinatorial effect of activated biological pathways acting synergistically with the substrate of subclinical atherosclerosis. High-sensitivity C-reactive protein hs-CRP [8,9] and other markers such as fibrinogen [10,11] and lipoprotein(a) [12] present a high level of evidence for association with CAD.

Moreover, several studies have demonstrated a relationship between the presence of carotid artery disease and coronary artery disease

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because both arterial beds share the same risk factors that contribute to the progression of atherosclerosis [13]. In fact, the carotid intima–media thickness (IMT) has shown to be a good index of the presence and extent of coronary disease [14], and its measure provides incremental prognostic information over and above that provided by traditional risk factor assessment in subjects with an intermediate risk estimate based on the Framingham score [15].

In this prospective study we assessed the relation of traditional cardiovascular risk factors, hs-CRP, fibrinogen, lipoprotein(a), IMT and carotid plaque, with the severity and prognostic localization of coronary artery lesions, in subjects without known cardiovascular disease undergoing first coronary angiography.

2. Methods

2.1. Study population

We considered all consecutive subjects admitted to our catheterization laboratory from September 2013 to February 2015 who underwent first coronary angiography.

They were referred because of the onset of stable angina with a positive stress test or imaging study demonstrating inducible ischemia. Patients with significant valvular disease, heart failure, previous myocardial infarction or acute coronary syndrome were excluded.

We also excluded subjects expected to show raised circulating C-reactive protein levels such as those with any chronic inflammatory diseases, rheumatoid arthritis or systemic lupus erythematosus, as well as patients taking immunosuppressant agents, glucocorticoids, or with cirrhotic liver disease that may blunt the production of C-reactive protein, leading to lower circulating levels.

Finally, patients who had previously undergone carotid endarterectomy or carotid angioplasty, and patients who had completely occluded carotid arteries were also excluded.

The study was approved by the Hospital Ethics Committee and each patient provided written informed consent.

2.2. Characterization of traditional risk factors

For the evaluation of traditional risk factors (RF), such as diabetes, hypertension, dyslipidemia, smoking and family history of coronary heart disease, we used the most currently used definition [16].

Briefly, diabetes mellitus was diagnosed if fasting blood glucose was at least 126 mg/dL, or if the subject was on oral hypoglycemic drugs or insulin, or had at least 6.5% of HbA1c.

Diagnosis of hypertension was based on the presence of systolic blood pressure of at least 140 mm Hg and/or diastolic blood pressure of at least 90 mm Hg, or use of antihypertensive medication.

Hypercholesterolemia was diagnosed if serum low-density lipoprotein (LDL) cholesterol was at least 130 mg/dL or in case of use of lipid-lowering drugs.

For smoking habit we considered people smoking at least one cigarette per day and people who had a previous history of smoking. Finally, family history of coronary heart disease was defined in presence of atherosclerotic cardiovascular disease or death from cardiovascular disease in a first degree relative prior to age 55 (male) or 60 (female).

2.3. Characterization of plasma profile markers

Venous blood was drawn in the morning after an overnight fast.

We measured circulating concentrations of the following biomarkers: hs-CRP (an acute phase protein playing a key role in inflammation), fibrinogen (an important hemostatic factor) and lipoprotein(a) (the protein in the lipid profile showing the strongest genetic determination).

These markers were measured with standardized assays and with excellent reproducibility.

Hs-CRP was assayed on serum using a nephelometric method on the Siemens DADE Behring BN II analyzer.

Fibrinogen concentration was determined on fresh plasma (obtained by centrifugation of whole blood at 2000 × *g* for 15 min), using a coagulation analyzer with its accompanying reagent (STA-R device with STA-R reagent, Diagnostica Stago, Asnières, France) and electromechanical readout. The device was calibrated with Fibrinogen Calibrator Standard 1 through 6 (Siemens Healthcare Diagnostics, Marburg, Germany) and STA-R reagent in normal clinical routine.

Lipoprotein(a) was assayed on serum Siemens reagent on a Siemens BNII nephelometer (Siemens Healthcare Diagnostics, Newark, Delaware).

Elevated levels of hs-CRP were defined if >3 mg/L [17–18].

Lipoprotein(a) levels <30 mg/dL [19–20] and a plasma fibrinogen <300 mg/dL were defined as being normal [21–22].

2.4. Carotid ultrasound evaluation

All studies were performed using a Philips EPIQ 5G Ultrasound System equipped with an L12-3 broadband linear array, by a single experienced vascular sonographer unaware of clinical and angiographic features of subjects.

Transverse and longitudinal scans were obtained on the common carotid artery, the carotid bifurcation, and the internal and external carotid artery by B-mode and color Doppler ultrasound.

IMT was measured in a semi-automatic way and defined as the distance between the leading edges of the lumen–intima and the media–adventitia echoes [23]. Mean IMT was defined as the average of the IMT values of the far wall in the left and right carotid arteries. For each subject, the maximum carotid IMT was imaged for the near and far wall of each common carotid artery, carotid bifurcation, and internal carotid artery. A value >0.9 mm was considered abnormal according to European Guidelines on Cardiovascular Disease Prevention in clinical practice [24].

In our study, the major parameter used was the presence of a lesion on common carotid artery, carotid bifurcation and internal carotid artery producing a 50% diameter stenosis with a peak systolic velocity (PSV) >125 cm/s, defined as significant carotid disease (SCD) [25,26].

2.5. Coronary angiography and Syntax Score assessment

Selective coronary angiograms were obtained by the Judkins technique.

Multiple views were recorded and evaluated applying a cardiovascular angiographic analysis system before and after intracoronary injection of nitroglycerin.

For angiographic analysis, we used the Syntax Score, widely accepted as a coronary artery disease complexity marker, as well as a prognostic index [27–29].

Based on the baseline diagnostic angiogram, each coronary lesion producing >50% diameter stenosis in segments ≥1.5 mm was scored separately, and added together to provide the overall Syntax Score.

The score of patients was independently assessed by two experienced interventional cardiologists who were blinded to the carotid-ultrasound data.

Presence of CAD was defined if a Syntax Score different from 0 was found.

Finally, every patient was assigned to one of three categories according to the value of the Syntax Score: low (<22), intermediate (between 23 and 32), and high (>32).

We defined prognostic localization of CAD when either a stenosis (>50%) on the left main (LM) and/or proximal left anterior descending (LAD), up to the first diagonal branch, was found [30].

2.6. Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range, IQR) and compared with Student's *t*-test or Mann–Whitney or Wilcoxon tests, on the basis of the normality of the data (which was verified by the Kolmogorov–Smirnov goodness-of-fit test).

Categorical variables (such as frequencies or percentage) were compared with χ^2 test with Yates correction for continuity or the Fisher exact test as appropriate for the available data.

First we evaluated the association of conventional risk factors, plasma profile markers and SCD with the presence or absence of CAD.

Then we analyzed the association of all risk factors previously cited with the three classes of Syntax Score and with the prognostic localization of CAD.

Two-side *p*-values <0.05 were considered statistically significant.

Only variables that showed a significant association at univariate analysis were entered into the multivariate model.

To avoid multicollinearity, a "low-noise model" has been researched in which each predictor variable correlates at most only minimally with the other. Selection of the variables included in the multivariate model was done with backward elimination (Wald statistic, confirmed using forward and stepwise selection) based on covariates listed in Tables 3 and 4. Only the covariates that were significantly associated with the risk of composite efficacy endpoint at univariate analysis ($p < 0.05$ for model inclusion and $p > 0.10$ for exclusion) and considered clinically relevant were included, and the convention of limiting the number of independent variables to 1 for every 10 events was followed [31,32]. The results are reported as adjusted odds ratio (ORs) with associated 95% confidence intervals (CI).

The statistical analyses were performed using SPSS 16.0.2 (SPSS Inc., Chicago, IL, USA).

3. Results

During the index period a total of 574 patients (mean age of 60.1 ± 6.7 years, mean European-SCORE of 6.5%) were included in our study: 490 subjects (85%) had CAD, while 84 subjects (15%) had normal coronary arteries. Characteristics of study population are shown in Table 1.

In the CAD population, low, intermediate and high Syntax Score was found in 243 (49.6%), 131 (26.7%) and 116 (23.7%) patients, respectively.