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Routine laboratory tests to risk-stratify patients with chronic coronary artery disease

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ABSTRACT

Background: Several biohumoral variables, taken individually, are predictors of prognosis in patients with chronic coronary artery disease (CAD). We hypothesized that taken together, laboratory tests provide prognostic information that is additive to a complete diagnostic work-up.
Methods: We prospectively examined 2370 consecutive patients with chronic CAD, as shown by a >50% coronary stenosis (in 95% of patients), previous coronary revascularization (in 31% of patients), and/or previous myocardial infarction (MI, in 54% of patients). We tested the ability of laboratory and clinical variables to predict future cardiac events (cardiac death and non-fatal MI).
Results: During follow-up (median, 46 months), 147 patients (6.2%) died from cardiac causes and 81 (3.4%) experienced a non-fatal MI. Using multivariate analysis, after adjustment for clinical variables (including left ventricular ejection fraction and angiographic extent of coronary stenoses), a high-density lipoprotein cholesterol (HDLc) concentration < 35 mg/dL ($p < 0.0001$), a neutrophil-to-lymphocyte ratio >2.4 ($p = 0.0014$), and an fT3 serum level < 2.1 pg/mL with normal thyrotropin (low-T3 syndrome) ($p = 0.0260$) showed an independent and incremental prognostic value, and were associated with an increase in the rate of cardiac events of 86%, 57% and 41%, respectively. When these variables were added to clinical and instrumental variables, the prognostic power of the model increased significantly (global chi-square improvement: from 157.01 to 185.07, $p < 0.0001$).
Conclusion: Low HDLc, high neutrophil-to-lymphocyte ratio and low-T3 syndrome, both individually and taken together, provide prognostic information that is independent of and incremental to the main clinical and instrumental findings.

Introduction

In the management of patients with chronic CAD, laboratory tests are performed very frequently in order to identify biohumoral cardiovascular risk factors, to monitor their trends, to assess the effectiveness and safety of therapy, and preliminary to invasive investigations and contrast media administration [1]. Various studies have examined the effect of individual biohumoral variables on the prognosis of patients with chronic CAD. We tested the hypothesis that laboratory tests, taken together, provide additional prognostic information in patients with chronic CAD, and that this information is independent of and incremental to commonly analyzed clinical and instrumental variables.

Methods

Patients

Of 8522 patients admitted to the Cardiology Unit of our Institute between 2001 and 2007, we prospectively studied a group of consecutive patients at their first hospital admission for chronic CAD. Inclusion criteria were: (a) history of stable angina or the evidence of inducible myocardial ischemia associated with coronary stenoses that reduced the lumen of one or more coronary arteries by >50%, (b) previous coronary artery bypass graft surgery, (c) previous percutaneous coronary intervention, and/or (d) the documentation of a previous myocardial infarction (MI) by clinical records. Out of 2871 patients initially screened, we excluded 373 patients for a clinical course compatible with an acute MI, 36 patients in whom the final diagnosis was cardiomyopathy or myocarditis, 33 patients for associated valvular heart disease of at least moderate entity, 10 patients for chronic renal failure under hemodialysis treatment and

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Table 1
Clinical characteristics of patients.

Patient characteristics	Overall $n = 2370$	With events $n = 228$	Without events $n = 2142$	p-Value
Age, mean (SD), years	67 (10)	70 (9)	67 (10)	**<0.0001**
Male, *n* (%)	1865 (79)	183 (80)	1682 (79)	0.542
Family history of premature CAD, *n* (%)	1144 (48)	103 (45)	1041 (49)	0.325
Diabetes mellitus, *n* (%)	628 (26)	86 (38)	542 (25)	**<0.0001**
Hypertension, *n* (%)	1435 (60)	138 (61)	1297 (61)	0.994
Hypercholesterolemia, *n* (%)	1663 (70)	140 (61)	1523 (71)	0.0023
Obesity, *n* (%)	663 (28)	55 (24)	608 (28)	0.172
Smoker in the last year, *n* (%)	1165 (49)	104 (46)	1061 (50)	0.260
Previous myocardial infarction, *n* (%)	1269 (54)	147 (64)	1122 (52)	**0.0005**
Exertional angina, *n* (%)	627 (26)	45 (20)	582 (27)	**0.0176**
Angina at rest, *n* (%)	438 (19)	41 (18)	397 (19)	0.8584
Mixed angina, *n* (%)	689 (29)	71 (31)	618 (29)	0.4901
Previous coronary artery bypass surgery, *n* (%)	284 (12)	52 (23)	232 (11)	**<0.0001**
Previous percutaneous coronary interventions, *n* (%)	456 (19)	47 (21)	409 (19)	0.580
Left ventricular ejection fraction, mean (SD), %	52 (11)	44 (14)	52 (11)	**<0.0001**
Disease of one coronary vessel, *n* (%)	841 (36)	48 (21)	793 (37)	**<0.0001**
Disease of two coronary vessels, *n* (%)	602 (25)	72 (32)	530 (25)	**0.0253**
Disease of three coronary vessels, *n* (%)	404 (17)	58 (25)	346 (16)	**0.0005**
Disease of the left main stem, *n* (%)	234 (10)	36 (16)	198 (9)	**0.0025**
Disease of secondary vessels only, *n* (%)	175 (7)	9 (4)	166 (8)	**0.0443**
Non-significant stenosis, *n* (%)	114 (5)	5 (2)	109 (5)	0.0706

CAD, coronary artery disease.
Bold values have been utilized to indicate statistically significant variables.

9 patients for overt hyperthyroidism. During hospitalization, each patient had undergone a diagnostic work-up that included laboratory testing, two-dimensional echocardiography, and coronary angiography. The characteristics of the 2370 patients studied are illustrated in Table 1.

The criteria used to define diabetes mellitus, arterial hypertension, hypercholesterolemia and obesity were consistent with international guidelines [2–4]. The left ventricular (LV) ejection fraction was measured by two-dimensional echocardiography using the single-plane or the biplane Simpson's rule. After reading the coronary arteriography, each patient was assigned an angiographic score whereby 1 = single vessel disease, 2 = two-vessel disease, 3 = three-vessel disease, 4 = disease of left main stem, 0.5 disease of secondary vessels only, and 0 = absence of significant coronary stenoses [5]. The LV ejection fraction was <35% in 13% of patients, and ranged between 35 and 50% in 24% of patients. A multi-vessel coronary artery disease or a stenosis of the left main stem were present in 52% of patients.

Laboratory tests

The first day of hospital admission, samples of peripheral venous blood were drawn from the antecubital vein after patient overnight fasting, and processed for a complete series of routine laboratory assays. The laboratory variables explored were hematocrit, white blood cell (WBC) count, neutrophil-to-lymphocyte (N/L) ratio, platelet count, fasting glucose, serum creatinine, total cholesterol, high-density lipoprotein cholesterol (HDLc), triglycerides, TSH, fT3, fT4, and C-reactive protein. Low-density lipoprotein cholesterol (LDLc) concentration was calculated using the Friedewald equation [6]. The glomerular filtration rate (eGFR) was estimated according to the Cockcroft–Gault formula [7]. All laboratory tests were analyzed as categorical variables based on the normal values of our laboratory or previous studies. Although in current guidelines the cut-off value for low HDLc is 40 mg/dL [8], we considered a cut-off value of 35 mg/dL [9] because HDLc concentrations below this threshold were more strictly associated with cardiac events in our patient population. The cut-off value of serum creatinine was set to 1.4 mg/dL [10,11]. The cut-off value of eGFR was set to 30 mL/min. Low T3 syndrome was defined as fT3 serum level < 2.1 pg/mL without accompanying TSH increase, hypothyroidism was defined as TSH > 3.8 μIU/mL [12]. An N/L ratio of 2.42 was chosen on the basis of previous studies from the same institution [13].

Follow-up

The entire group of patients was followed for up to 7 years (median, 46 months). Patients were followed-up by periodic examinations in the outpatient setting. In patients who did not attend this program, follow-up data were obtained using a written telephone interview (administered to the patient or the patient's family by dedicated personnel) or mail questionnaires. In case of negative answers, the local demographic registry was queried. Cardiac death was defined as death caused by acute MI, death caused by heart failure, or sudden and unexpected death not related to any possible cause. The diagnosis of non-fatal MI was documented by clinical records. The study protocol was approved by the local committee on human research. In addition, patients gave written informed consent to have their clinical data prospectively collected for research purposes.

Statistical analysis

Continuous variables were expressed as mean and SD, categorical variables as percentages. The primary endpoint was the occurrence of cardiac events, defined as cardiac death or non-fatal MI. Predictors of survival were identified using univariate and multivariate analysis, performed using the Cox proportional hazards regression model. Categorical variables were included in the model as dummy variables. Only those variables resulting significant at univariate analysis were entered into the regression model; the significant variables at multivariate analysis were selected using a backward elimination procedure. Analysis was initially limited to the clinical and instrumental variables. Thereafter, laboratory variables were examined, both before and after adjustment for the independent clinical and instrumental predictors of survival, as well as for medical treatment and myocardial revascularization. The incremental prognostic information obtained after including laboratory variables was evaluated by the chi-square. All statistical tests were two-tailed; a p-value < 0.05 was considered significant. Statistical analysis was performed with the software program JMP 9 [SAS Institute Inc.] and R: A Programming Environment for Data