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CLINICAL RESEARCH STUDY

N-Terminal Probrain Natriuretic Peptide and C-reactive Protein in Stable Coronary Heart Disease

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ABSTRACT

PURPOSE: C-reactive protein (CRP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) provide prognostic information in patients with stable coronary heart disease. The aim of the study was to investigate whether combined use of NT-proBNP and CRP improves risk stratification in these patients.
METHODS: This cohort study included 989 patients with stable coronary heart disease who underwent coronary stenting. CRP and NT-proBNP were measured before angiography. The primary end point of the study was all-cause mortality. Using median values of NT-proBNP (279.9 ng/L) and CRP (1.2 mg/L), patients were divided into 4 groups: low NT-proBNP-low CRP group (305 patients with NT-proBNP<median and CRP<median); low NT-proBNP-high CRP group (190 patients with NT-proBNP<median and CRP≥median; high NT-proBNP-low CRP group (237 patients with NT-proBNP≥median and CRP<median); and high NT-proBNP-high CRP group (257 patients with NT-proBNP≥median and CRP≥median).
RESULTS: During a median follow-up of 3.6 years (interquartile range 3.3 to 4.5 years), there were 85 deaths: 6 deaths in the low NT-proBNP-low CRP group, 11 deaths in the low NT-proBNP-high CRP group, 20 deaths in the high NT-proBNP-low CRP group, and 48 deaths in the high NT-proBNP-high CRP group with Kaplan-Meier mortality estimates of 2.7%, 8.9%, 12.1% and 35.6%, respectively ($P < .001$). Cox proportional hazards model showed that combination NT-proBNP-CRP was the strongest independent correlate of mortality (hazard ratio [HR] 4.3, 95% confidence interval [CI], 2.0-9.3; $P < .001$ for high NT-proBNP-high CRP vs low NT-proBNP-low CRP).
CONCLUSION: Combined use of NT-proBNP and CRP improves long-term risk prediction of mortality in patients with stable coronary heart disease.

KEYWORDS: N-terminal pro-brain natriuretic peptide; C-reactive protein; Coronary heart disease; Mortality

Stable coronary heart disease is the most frequent form of ischemic heart disease, and coronary stenting is a common treatment in these patients. Two population-based studies in the US population have reported that annual rates of myocardial infarction in patients with angina were 3% to 3.4%,[1,2] allowing an estimation of 30 patients with angina for each hospitalized patient with acute myocardial infarction. Taking into consideration that 550 000 patients with acute myocardial infarction are hospitalized annually,[3] it has been estimated that up to 16.5 million persons in the United States have chronic stable angina.[4] Application of biomarkers that reliably predict prognosis in such a large group of patients with ischemic heart disease is of paramount clinical importance. Several studies have indicated that increased levels of C-reactive protein (CRP) predict rapid progression of coronary artery disease[5] or increased risk of death in patients with stable angina.[6,7] Recently, N-terminal probrain natriuretic peptide (NT-proBNP) also has been shown to be a strong predictor of mortality in patients with stable coronary heart disease.[8,9] In patients with acute coronary syndromes, a multimarker approach to risk stratification

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has allowed a powerful short- and long-term prediction of heightened risk of death,[10,11] myocardial infarction, and congestive heart failure.[10] Although information available indicates that NT-proBNP and CRP provide unique prognostic information in patients with stable ischemic heart disease, no studies so far have assessed whether combined use of these biomarkers improves the risk stratification regarding mortality.

We undertook this study to investigate whether combined use of NT-proBNP and CRP improves the risk stratification regarding mortality or other major cardiac events in a large series of patients with stable coronary heart disease after coronary stenting over a long-term follow-up. The hypothesis for the study was that combined use of these biomarkers may provide a better risk stratification in patients with stable coronary heart disease than each of the biomarkers alone.

CLINICAL SIGNIFICANCE

- N-terminal probrain natriuretic peptide and C-reactive protein provide, separately, prognostic information in patients with stable coronary heart disease.
- The present study shows that elevation of both N-terminal probrain natriuretic peptide and C-reactive protein in patients with stable coronary heart disease is associated with a poorer 5-year prognosis than isolated elevation of each of these biomarkers.
- Combined use of N-terminal probrain natriuretic peptide and C-reactive protein provides better prognostic information compared with the use of each of these biomarkers alone.

METHODS

Patients

Between September 1999 and February 2002, 1059 patients with stable coronary artery disease underwent coronary angiography with stent implantation in the Deutsches Herzzentrum and Klinikum rechts der Isar in Munich and were recruited in a prospective cohort study to investigate the prognostic value of biochemical biomarkers. Results for prognostic value of NT-proBNP in these patients have been reported.[9] Patients with congestive heart failure with a New York Heart Association (NYHA) class III and IV (70 patients) were excluded. Nine hundred eighty-nine patients with angiographic confirmation of stable coronary artery disease make up the cohort for the present study. The diagnosis of stable coronary artery disease was based on the presence of angina symptoms—in a patient already diagnosed to have coronary artery disease—that were occurring without a change in their pattern during the preceding 2 months. Patients with acute coronary syndromes diagnosed on the basis of characteristics of anginal status, electrocardiographical changes or increased levels of creatine kinase MB or cardiac troponin were not included in the study. Furthermore, patients with advanced renal disease, acute inflammatory states, or malignancies were excluded. All patients gave informed consent before recruitment in the study. The study protocol was approved by the institutional ethics committee.

Definitions

Coronary artery disease was diagnosed in the presence of coronary stenoses ≥50% lumen obstruction in at least one of the three major coronary arteries. Congestive heart failure was graded according to New York Heart Association (NYHA) Classification. Angina was graded according to the Canadian Cardiovascular Society classification system.[12] Arterial hypertension was defined in the presence of active treatment with antihypertensive agents or otherwise as a systolic blood pressure of more than 140 mm Hg or diastolic blood pressure of more than 90 mm Hg at least on 2 separate occasions. Hypercholesterolemia was defined as a documented total cholesterol value equal to or >240 mg/dL before initiation of statin therapy. Smokers were defined as those currently smoking any tobacco. Diabetes mellitus was defined if patients were under an active treatment with insulin or oral hypoglycemic agents. For patients on dietary treatment alone, documentation of abnormal fasting blood glucose or glucose tolerance test according to the World Health Organization criteria were required for the diagnosis of diabetes.[13]

Biochemical Measurements

Blood was collected before angiography in tubes containing ethylenediaminetetraacetic acid (Sarstedt, Nümbrecht, Germany) and promptly centrifuged at 1550 g for 10 minutes. After separation, plasma aliquots were stored frozen at −80°C until assayed within batches. Blood count, serum lipids, and other metabolites were determined immediately after collection using standard methods.

NT-proBNP measurements were performed on a Roche Elecsys 1010 automated analyser (Roche Diagnostics, Mannheim, Germany). The Roche NT-proBNP sandwich electrochemiluminescent assay uses 2 polyclonal antibodies that recognize epitopes located in the N-terminal part (1-76 amino acid residues) of proBNP (1-108 amino acid residues). The measuring range, defined by the lower detection limit and the maximum of the master curve, provided by the manufacturer is 5-35 000 ng/L. The functional sensitivity, or the lowest analyte concentration that can be reproducibly measured with a between-run coefficient of variation of 20%, is <50 ng/L. NT-proBNP concentrations in healthy subjects depend on age and sex. In women, the 95th percentile of NT-proBNP concentration increases from 152 pg/mL (at <55 years of age) to 265 pg/mL (at >65 years of