Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 45, No. 2, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2004.09.060

Pregnancy-Associated Plasma Protein-A Levels in Patients With Acute Coronary Syndromes

Comparison With Markers of Systemic Inflammation, Platelet Activation, and Myocardial Necrosis

Christopher Heeschen, MD,* Stefanie Dimmeler, PHD,* Christian W. Hamm, MD, FACC,† Stephan Fichtlscherer, MD,* Maarten L. Simoons, MD, FACC,‡ Andreas M. Zeiher, MD, FACC,* for the CAPTURE Study Investigators

Frankfurt and Bad Nauheim, Germany; and Rotterdam, the Netherlands

OBJECTIVES The goal of this study was to determine the predictive value of pregnancy-associated plasma protein-A (PAPP-A) in patients with acute coronary syndromes (ACS).

BACKGROUND Pregnancy-associated plasma protein-A is a zinc-binding matrix metalloproteinase abundantly expressed in eroded and ruptured plaques and may serve as a marker of plaque destabilization.

METHODS In 547 patients with angiographically validated ACS and in a heterogeneous emergency room population of 644 patients with acute chest pain, respectively, PAPP-A as well as markers of myocardial necrosis (troponin T [TnT]), ischemia (vascular endothelial growth factor [VEGF]), inflammation (high-sensitivity C-reactive protein [hsCRP]), anti-inflammatory activity (interleukin [IL]-10), and platelet activation (soluble CD40 ligand [sCD40L]) were determined. Patients were followed for the occurrence of death or myocardial infarction.

RESULTS In patients with ACS, elevated PAPP-A levels (>12.6 mIU/l) indicated an increased risk (odds ratio 2.44 [95% confidence interval (CI) 1.43 to 4.15]; p = 0.001). When the analysis was restricted to TnT-negative patients, PAPP-A still identified a subgroup of high-risk patients (odds ratio [OR] 2.72 [95% confidence interval (CI) 1.25 to 5.89]; p = 0.009). In a multivariable model, PAPP-A (OR 2.01; p = 0.015), sCD40L (OR 2.37; p = 0.003), IL-10 (OR 0.43; p = 0.003), and VEGF (OR 2.19; p = 0.018) were independent predictors. Prospective validation in patients with chest pain confirmed that PAPP-A levels reliably identify high-risk patients (adjusted OR 2.32 [95% CI 1.32 to 4.26]; p = 0.008). Patients negative for all three markers (TnT, sCD40L, and PAPP-A) were at very low cardiac risk (30 days: 3.0% event rate; no death).

CONCLUSIONS The PAPP-A level as a marker of plaque instability is a strong independent predictor of cardiovascular events in patients with ACS. Simultaneous determination of biomarkers with distinct pathophysiological profiles appears to remarkably improve risk stratification in patients with ACS. (J Am Coll Cardiol 2005;45:229–37) © 2005 by the American College of Cardiology Foundation

Elevated levels of circulating cardiac troponin, a marker of myocardial necrosis, are found in about one-third of the patients with acute coronary syndromes (ACS) and are associated with an increased short-term risk of death and nonfatal myocardial infarction (1–4). Although the absolute short-term risk in troponin-negative patients is significantly lower as compared with troponin-positive patients, the large number of patients without troponin elevation remains clinically challenging with respect to risk assessment and therapeutic management. Specifically, the six-month risk of death or nonfatal myocardial infarction in troponin-negative patients was 8.4% in the c7E3 Anti Platelet Therapy in Unstable Refractory angina (CAPTURE) trial (5). Therefore, the simultaneous measurement of several biomarkers that reflect distinct pathophysiologic processes may improve risk stratification in patients without evidence for myocardial necrosis (6).

Convincing evidence suggests that both inflammatory as well as thrombotic mechanisms are involved in the pathophysiology of patients with ACS (7). The availability of a sensitive and specific early marker of plaque instability, whose levels become elevated before or even in the absence of myocardial necrosis, should improve diagnostic and therapeutic decision-making. Pregnancy-associated plasma protein-A (PAPP-A) is a high-molecular-weight, zinc-binding matrix metalloproteinase belonging to the metzincin superfamily of metalloproteinases (8,9) and was originally identified in the plasma of pregnant women (10). It is widely used for the screening of fetal trisomy in the first trimester of gestation; PAPP-A was also found to be abundantly expressed in eroded and ruptured plaques, respectively, but is only minimally expressed in stable plaques (11). However, a very recent study indicates that, even in patients with stable coronary heart disease, PAPP-A levels are associated with angiographic plaque complexity (12) and were suggested to predict recurrence of symptoms in pa-

From *Molecular Cardiology, Department of Internal Medicine III, University of Frankfurt, Frankfurt, Germany; †Kerckhoff Heart Center, Bad Nauheim, Germany; and ‡Erasmus University, Thoraxcentre, Rotterdam, the Netherlands. Trial participants have been published previously (see reference 17).

Manuscript received July 9, 2004; revised manuscript received September 22, 2004, accepted September 27, 2004.

JACC Vol. 45, No. 2, 2005
January 18, 2005:229–37

Abbreviations and Acronyms

ACS	= acute coronary syndromes
CAPTURE c7E3	= Anti Platelet Therapy in Unstable Refractory Angina trial
CI	= confidence interval
hsCRP	= high-sensitivity C-reactive protein
IL	= interleukin
PAPP-A	= pregnancy-associated plasma protein A
ROC	= receiver operating characteristic
sCD40L	= soluble CD40 ligand
TnT	= troponin T
VEGF	= vascular endothelial growth factor

tients with ACS (13). However, the precise role of circulating PAPP-A plasma levels for predicting hard end points like death or myocardial infarction in patients with ACS remains to be determined. Most importantly, whether PAPP-A plasma levels indeed provide additive and independent prognostic information compared with recently established biomarkers in patients with ACS is entirely unknown. Therefore, we compared the prognostic significance of PAPP-A plasma levels with markers of systemic inflammation, platelet activation, ischemia, and myocardial necrosis in two distinct study populations, a high-risk population with refractory ACS and a large heterogeneous group of patients with chest pain (6,14–16).

METHODS

Clinical trial population of patients with ACS. The CAPTURE trial included patients with recurrent chest pain at rest associated with electrocardiographic changes during treatment with intravenous heparin and glyceryl trinitrate (17). All patients underwent coronary angiography before randomization, indicating significant coronary artery disease with a culprit lesion ≥70% suitable for angioplasty. Heparin was administered from before randomization until at least 1 h after the percutaneous coronary intervention. For all patients, coronary angioplasty was scheduled between 18 and 24 h after beginning study treatment. The patients were randomly assigned to treatment with the glycoprotein IIb/IIIa receptor antagonist abciximab or placebo. Because other markers, such as troponin T (TnT) (5,18) and soluble CD40 ligand (sCD40L) (6), have been shown to interact with the treatment effect of abciximab, we separately analyzed patients with available blood samples enrolled in the placebo arm (n = 547; 86% of placebo patients) and patients enrolled in the abciximab arm (n = 547; 87% of abciximab patients). For all patients, the first available blood sample collected after a mean time of 8.7 ± 4.9 h after onset of symptoms was analyzed.

Emergency room population of patients with acute chest pain. A heterogeneous group of 626 consecutive patients with acute chest pain (161 females and 465 males, mean age 61 years [range 38 to 82 years]) presenting to the emergency room at the University of Hamburg with acute chest pain lasting less than 12 h. Patients with characteristic ST-segment elevations were excluded. The presence of coronary artery disease was documented by one of the following criteria: electrocardiographic evidence of myocardial ischemia (new ST-segment depression or T-wave inversion), a history of coronary heart disease (myocardial infarction or coronary revascularization, a positive exercise stress test, or narrowing of at least 50% of the luminal diameter of a major coronary artery on a current angiogram). Patients without coronary heart disease had to have a normal coronary angiogram. Blood samples were collected at the time of arrival in the emergency room (5.1 ± 3.4 h after onset of symptoms before initiation of treatment), and a second blood sample was drawn 4 h later.

Biochemical analysis. Determination of the cardiac markers was performed blinded to the patients' histories and the allocated treatment at the research laboratory of the University of Frankfurt. High-sensitivity interleukin (IL), vascular endothelial growth factor (VEGF), and sCD40L were measured by ELISA (both R&D Systems, Wiesbaden, Germany). We used the following, previously established diagnostic threshold values: 5.0 μg/l for sCD40L, 300 ng/l for VEGF, and 3.5 ng/l for IL-10 (6,14,15). Cardiac TnT and PAPP-A were determined using a one-step enzyme immunoassay based on electrochemiluminescence technology (Elecsys 2010, Roche Diagnostics, Mannheim, Germany). Using internal controls, total imprecision for PAPP-A over the eight-week period was 8.5%. High-sensitivity C-reactive protein (hsCRP) was measured using the Behring BN II Nephelometer (Dade-Behring, Deerfield, Illinois). A diagnostic threshold value of 10 mg/l was used (16,19).

Statistical methods. A logistic regression model was used to estimate the relative risk for cardiovascular events, and patients were categorized in quintiles of PAPP-A levels (20). Primary end points were mortality and nonfatal myocardial infarction after 30 days (chest pain study) and 6 months (CAPTURE trial), respectively. For each time point (24 h, 72 h, 30 days, and 6 months), the logistic regression model was used to estimate the relative risk for death and myocardial infarction. Post-hoc analysis of PAPP-A quintiles was performed using the logistic regression model, with PAPP-A quintiles as a categorical variable, and the first quintile served as the reference group. Receiver operating characteristics (ROC) curve analysis over the dynamic range of the PAPP-A assay was used to identify the threshold level for PAPP-A providing the highest predictive value. Cumulative survival was univariately evaluated by Kaplan-Meier analysis (log-rank test). The effect of baseline characteristics (with $p = 0.10$ necessary to enter a variable into the model) and other biochemical markers on any observed associations between PAPP-A levels and cardiovascular events was analyzed using stepwise logistic regression models. All results for continuous variables are expressed as means ± SD. Continuous variables were tested