Circulating Pregnancy-Associated Plasma Protein A Predicts Outcome in Patients With Acute Coronary Syndrome but No Troponin I Elevation

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Background—Risk stratification in troponin (cTn)-negative acute coronary syndrome (ACS) remains a clinical challenge. We investigated the predictive value of circulating pregnancy-associated plasma protein A (PAPP-A), a novel marker of atherosclerotic plaque activity, in these patients.

Methods and Results—Two hundred consecutive hospitalized ACS patients were included, of whom 136 (69 men and 67 women; mean±SD age, 66±16 years) remained cTnI-negative for up to 24 hours. PAPP-A was measured at admission, 6 to 12 hours, and 24 hours. During 6-month follow-up, 26 (19.1%) of the cTnI-negative patients reached a primary end point (cardiovascular death, myocardial infarction, or revascularization). At a cutoff level of 2.9 mIU/L, elevated PAPP-A was an independent predictor of adverse outcome (adjusted risk ratio [RR], 4.6; 95% confidence interval, 1.8 to 11.8; P=0.002). Another independent predictor was admission CRP >2.0 mg/L (RR, 2.6; P=0.03).

Conclusions—Measurement of plasma PAPP-A, a zinc-binding matrix metalloproteinase, is a strong independent predictor of ischemic cardiac events and need of revascularization in patients who present with suspected myocardial infarction but remain troponin negative. (Circulation. 2003;108:1924-1926.)

Key Words: proteins ■ plasma ■ pregnancy ■ atherosclerosis ■ prognosis

Elevated cardiac troponins (cTn) and C-reactive protein (CRP) are associated with an increased risk of further cardiovascular events and death in patients with acute coronary syndromes (ACS).1-3 Although the absolute short- and mid-term risk in troponin-negative patients is much smaller than in the cTn-positive group, the high number of cTn-negative cases makes risk assessment in these patients clinically important.

Pregnancy-associated plasma protein A (PAPP-A) is a zinc-binding matrix metalloproteinase, which can be detected in the blood of patients with ACS and is then probably produced by vascular smooth muscle cells.4-6 PAPP-A is expressed in unstable but not in stable coronary artery plaques.5 In patients with myocardial infarction (MI), the release patterns of PAPP-A are highly variable, and marked increases in PAPP-A levels can appear as late as 30 hours after the onset of chest pain.7 The overall correlation with cTn levels appears to be poor.8 These observations led us to propose that elevated circulating PAPP-A, a marker of atherosclerotic plaque activity, might predict further clinical instability, infarction, and cardiac death, particularly in ACS subjects who remain cTn negative.

Methods

Subjects and Design

Two hundred consecutive patients presented to the emergency room of the Turku University Central Hospital for the evaluation of suspected ACS and gave their written informed consent to participate in the study. Sixty-three patients (31.5%) were found to be cTnI positive during the first 24 hours. One patient was excluded because of incomplete follow-up data. The final study population consisted of 136 TnI-negative patients (69 men, 67 women; mean±SD age, 66±16 years). All patients were treated according to routine clinical protocols.

The primary end point at 6 months was the combination of cardiovascular mortality, first episode of nonfatal MI, or revascularization (percutaneous coronary intervention or coronary artery bypass graft). Noncardiovascular death and hospitalization for unstable angina, worsening heart failure (congestive heart failure), or stroke were classified as secondary end points. Mortality data were obtained from Statistics Finland. Data of other end points were collected by telephone interviews and from the hospital records, which were retrospectively reviewed by 2 of the authors (J.L., T.I.) for classification. Occasional discrepancies were settled by mutual consensus of all authors. The local ethics committee approved the study.

Measurements

Serum samples for PAPP-A, cTnI, and CRP were collected immediately at admission. PAPP-A and cTnI were also measured at 6 to 12 and 24 hours. PAPP-A levels were determined post hoc by a point-of-care immunoassay, with a lower limit of detection of 0.5 mIU/L and a functional sensitivity (imprecision 20%) of 1.5 mIU/L. The between-assay imprecision at the lowest standard (2.5 mIU/L) was 13.7%. CRP was measured by an ultrasensitive AIO assay (Innotrac Diagnostics Corp) and cTnI, also...
using the Innontrac AIO, analytical sensitivity 0.05 μg/L, whereas the cutoff value at 10% imprecision (CV) was 0.22 μg/L. This level was used retrospectively to define cTnI negativity in this study. We chose 2.0 mg/L as the cutoff level for CRP. The clinicians had no access to the investigational AIO cTnI, CRP, or PAPP-A information.

Statistical Analysis

Categorical variables were compared between groups using the 2-tailed Fisher exact test. Continuous variables were compared with the use of Wilcoxon’s rank-sum test. The univariate and multivariate associations were analyzed using Cox’s proportional-hazards model to evaluate the independent contributions of the variables to the 6-month risk of cardiovascular events. The associations were quantified with risk ratios (RR) and 95% confidence intervals (95% CI). Survival curves were estimated using the Kaplan-Meier method, and differences between curves were tested with the log rank test. Correlations were tested using Spearman’s correlation test. SAS system for Windows release 6.12/1996 (Cary, NC) was used. Probability values <0.05 were considered significant.

**Results**

**PAPP-A and CRP Levels**

Median [25th, 75th percentiles] admission PAPP-A in the 136 cTnI-negative patients was 2.3 mIU/L [1.6, 3.0]. Sixty-four of 136 patients were discharged from the emergency room. The mean ±SD hospital stay in the remaining 72 patients was 4.3 ± 2.5 days. The highest detected PAPP-A was 2.35 mIU/L [1.6, 2.9] in discharged and 3.3 mIU/L [2.1, 6.5] in hospitalized patients (P<0.001). The median admission CRP was 2.1 mg/L [0.9, 8.1]. There was no correlation between CRP and either admission (r=−0.03, P=0.7) or highest detected (r=0.02, P=0.8) PAPP-A.

**Outcome at 6 Months**

There were 8 deaths (total mortality 5.9%) of which cardiovascular causes accounted for 5 (62.5%). Eight patients (5.9%) experienced MIs, 2 of which occurred late during the initial hospitalization. Thirteen patients (9.6%) underwent revascularization. There were 4 (2.9%) hospitalizations as a result of congestive heart failure, 7 (5.1%) as a result of unstable angina, and 1 for nonfatal stroke. At the end of the follow-up, 26 patients (19.1%) had met a primary and 12 (8.8%) a secondary end point.

**PAPP-A as a Predictor of Adverse Events**

In the 136 cTnI-negative subjects, PAPP-A 2.9 mIU/L (highest detected) was found to be the best cutoff value for the combined primary end point at 6 months (RR, 3.7; 95% CI, 1.6 to 8.9; P=0.0028). Patients were then divided into 4 groups according to the highest detected PAPP-A levels: <2.0, 2.0 to 2.8, 2.9 to 4.4, and ≥4.5 mIU/L. The Figure shows how the cumulative risk of a primary end point was only 8% if the highest detected PAPP-A was below 2.9 mIU/L, but increased to 25.0% if PAPP-A was 2.9 to 4.4 mIU/L (P=0.035) and to 37.9% if the level was >4.5 mIU/L (P=0.0012). Twenty of the 61 (33%) patients whose PAPP-A levels were ≥2.9 mIU/L suffered a primary end point. No statistically significant differences were found regarding any of the secondary end points. The Table shows the baseline clinical characteristics of the enrolled patients according to the highest detected PAPP-A level.

Only a single admission PAPP-A sample was available in 64 patients who were discharged from the emergency room. Among them, 17 (27%) patients had PAPP-A ≥2.9 mIU/L. The corresponding number of primary end points was 2 of 17 (12.0%), compared with 2 of 47 (4.2%) in patients with lower PAPP-A levels (RR, 2.8, P= not significant). Finally, we used only the admission PAPP-A value to predict outcome in the whole study group. Using the same cutoff value of 2.9 mIU/L, 12 of 40 (30.0%) versus 14 of 96 (14.6%) patients experienced a combined primary end point during the 6-month follow-up (RR, 2.3; 95% CI, 1.1 to 5.0; P=0.03). Thus, a single admission PAPP-A ≥2.9 mIU/L also showed a significant predictive value.

**Multivariate Analysis**

After adjusting for CRP, age, gender, diabetes (dietary or drug therapy), current smoking, hypertension, previous MI, and congestive heart failure (during index event), highest detected PAPP-A ≥2.9 mIU/L was found to be an independent predictor of a combined primary adverse event during the 6-month follow-up (adjusted RR, 4.6; 95% CI, 1.8 to

### Baseline Characteristics According to Prognostic PAPP-A Cutoff

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PAPP-A &lt;2.9 mIU/L (n=75)</th>
<th>PAPP-A ≥2.9 mIU/L (n=61)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64±13</td>
<td>69±13</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>35 (46.7)</td>
<td>34 (56.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (8.0)</td>
<td>13 (21.7)</td>
<td>0.027</td>
</tr>
<tr>
<td>Current smoker</td>
<td>21 (28.0)</td>
<td>11 (18.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (40.0)</td>
<td>34 (56.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous myocardal infarction</td>
<td>15 (20.0)</td>
<td>22 (36.7)</td>
<td>0.035</td>
</tr>
<tr>
<td>Aspirin</td>
<td>31 (41.3)</td>
<td>25 (41.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Warfarin</td>
<td>5 (6.7)</td>
<td>11 (18.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Statins</td>
<td>18 (24.0)</td>
<td>20 (33.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Killip class ≥2*</td>
<td>7 (9.3)</td>
<td>20 (33.3)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Plus/minus values are mean±SD; other values are number (percent), PAPP-A indicates pregnancy-associated plasma protein A; NS, not significant.

*During index hospitalization.
11.8; P=0.002). Another independent risk factor was admission CRP (RR, 2.6; 95% CI, 1.1 to 6.5; P=0.03). The adjusted risk ratio for previous MI almost reached statistical significance (RR, 2.3; 95% CI, 0.9 to 5.7; P=0.065).

Discussion

In cTn-negative ACS patients, PAPP-A levels ≥2.9 mIU/L were associated with a 4.6-fold higher adjusted risk of adverse outcome compared with patients whose circulating PAPP-A levels were <2.9 mIU/L. In patients with PAPP-A ≥4.5 mIU/L, the risk was even higher (RR, 6.9; 95% CI, 2.5 to 19.0; P<0.001) (Figure). Notably, 20 of 26 (77%) of all cardiovascular deaths, MIs, and revascularizations during the 6-month follow-up occurred in patients with PAPP-A ≥2.9 mIU/L.

Approximately two thirds of the patients who present with suspected MI have normal cTn, and one fourth have normal electrocardiograms, respectively. The 43-day risk of death or MI in cTn-negative patients has been estimated to be 3.9% and the incidence of revascularization 7.3%. In-hospital mortality in ACS patients who present with normal electrocardiograms can be as high as 5.7%. In our consecutive cTn-negative ACS patients, the cumulative 6-month mortality was 5.9% and the risk of all primary events was 19.1%. The Kaplan-Meier curves of event-free survival show that at 30 days, the cumulative event rate was 10.3% (Figure). Much of the further increase from 1 to 6 months was the result of the group with the highest baseline PAPP-A, probably with the most advanced forms of atherosclerosis. Thus, the short- to medium-term incidence of adverse events can be substantial in the so-called low-risk ACS population.

Sophisticated tools are not always available to perform individual risk stratification. Our results suggest that measurements of circulating PAPP-A can provide simple and efficient risk assessment in such patients. Even a single measurement of admission PAPP-A showed significant predictive power for the combined primary end point. Using the highest values over the first 24 hours, we were able to predict 3 of 4 adverse events that occurred during the following 6 months. However, the kinetics of PAPP-A release and the corresponding optimal sampling protocols in ACS remain to be determined.

PAPP-A is abundantly expressed in eroded and ruptured plaques, but not in stable plaques. It probably participates in the inflammatory reactions of the vascular wall, which lead to the disruption of the atherosclerotic plaque. Because PAPP-A is a matrix metalloproteinase, it could be involved in the processing of the plaque’s extracellular matrix and weakening of the fibrous cap. The fact that PAPP-A and CRP appear to be independent risk indicators points to different roles of the 2 in the events that lead to acute complications of coronary atherosclerosis.

To our knowledge, the present report is the first to show the predictive power of circulating PAPP-A in patients with atherosclerotic disease. As a point-of-care method, it could be used as a second test for risk stratification during the first 24 hours in cTn-negative patients to increase the safety of early discharge. The accumulation of adverse events in PAPP-A-positive (≥2.9 mIU/L) patients is quite rapid (Figure), and the Kaplan-Meier curves continue to diverge during the entire follow-up of 6 months. The use of elevated PAPP-A as a tool to guide therapy in such patients remains to be studied.

Acknowledgments

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References

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