plasma protein-A (PAPP-A) immunoassays developed for use during pregnancy to study acute coronary syndromes (ACS). That report and the authors’ related article in Clinical Chemistry (2) have important implications, because PAPP-A has been suggested to be a prognostic marker of cardiac risk (3). We have reported on the direct relationship between serum PAPP-A concentrations and both the extent and complex morphology of angiographic coronary artery stenoses in patients with chronic stable angina pectoris (4, 5). These studies were performed with the same assay that was used in the first clinical report on PAPP-A and ACS by Bayes-Genis et al., described a relationship between PAPP-A and unstable atherosclerotic plaques (3). This assay was based on a polyclonal capture antibody and a combination of monoclonal detection antibodies. It was calibrated with WHO reference standard 78/610, which was derived from serum collected from pregnant women. The findings of Qin et al. (1, 2), raise questions concerning the appropriateness of assays used in studies predicting cardiac risk. These authors have clearly demonstrated that the circulating molecular form of PAPP-A, with respect to its associated complexed protein (PAPP-A/proMBP), differs in ACS from the form that typically circulates at low concentrations in nonacute patients and at higher concentrations in pregnant women. The selection of a suitable combination of antibodies, directed against appropriate epitopes, is, therefore, paramount for developing assays for use in this setting. Recently, 2 highly sensitive assays have become available for PAPP-A, and have produced discordant findings in relation to ACS. It has been shown that the assay manufactured by DRG Co. (Germany) failed to detect any difference in serum PAPP-A concentrations between healthy controls and patients with ST-segment elevation myocardial infarction (6). By contrast, with the assay from Diagnostic System Laboratories, Inc. (DSL), PAPP-A concentrations predicted cardiovascular events after renal transplant (7) and cardiovascular events in patients who had presented to the emergency department with acute chest pain (8).

We compared the assay used by Bayes-Genis with the DSL assay in 61 patients with chronic stable angina, by use of serum collected immediately before diagnostic coronary angiography. Fasting blood samples were collected into Vacutainer® SST tubes. Serum was separated after clot development, <1 h after blood collection. Each sample was then divided into 3 fractions (to avoid freeze-thaw cycles) and frozen immediately at −80°C for storage. Specimens were frozen and thawed only once before analysis. We did not investigate the stability of PAPP-A in the SST tubes, and this was not remarked upon in either of the reports detailing the assay and analyte characteristics (4, 9) or within the manual provided by DSL. We found the limit of detection of the DSL assay to be in line with the manufacturer’s stated detection limit of 0.06 mIU/L and the within- and between-assay CVs were <3% and <8%, respectively, at concentrations of 2.5 and 10.0 mIU/L. The noncommercial assay had a detection limit of 0.03 mIU/L, and the within and between assay CVs were 10% and 15%, respectively. Details of the assay performance for these 2 assays have been described previously (4, 9). The correlation between the 2 assays (Spearman R) was 0.645 (Fig. 1A), and the analysis of residuals showed a mean difference of 6.33 (SD 2.34) mIU/L. A Bland-Altman plot (Fig. 1B) shows that these differences are positively skewed, with larger positive differences with higher mean PAPP-A values. Twenty-seven data points were below the limit of detection for the DSL assay and were not included in the statistical analysis. Both assays detected substantially higher PAPP-A concentrations in patients with coronary stenosis than in patients without stenosis. These major differences in assay performance may help explain the contrast in clinical findings observed when these 2 assays were used to investigate risk in patients with ACS.

Comment on Immunoassays

Developed for Pregnancy-Associated Plasma Protein-A (PAPP-A) in Pregnancy May Not Recognize PAPP-A in Acute Coronary Syndromes

To the Editor:

Qin et al. (1) recently discussed the limitations of pregnancy-associated
With the DSL assay (8), PAPP-A was reported as a specific and sensitive predictor of adverse cardiac events, with a clinical cutoff of 0.22 mIU/L (3), compared with 10 mIU/L with the noncommercial assay. Another report found a cutoff concentration of 2.9 mIU/L to be predictive of adverse cardiac event by use of a point of care assay (10).

The published studies on this topic have used a variety of antibodies, but all have used a calibrant based on the noncomplexed PAPP-A, which is found only in serum from individuals with ACS. There is potential for matrix interference and calibration bias with this assay arrangement. Paradoxically, there is substantial evidence from the clinical perspective, rather than from the theoretical laboratory approach, that PAPP-A is a useful prognostic marker in ACS. However, the findings of Qin et al. reinforce the need for assays based on antibodies that recognize noncomplexed PAPP-A that are calibrated using a defined calibrator of the noncomplexed form.

References


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