Coronary artery disease (CAD) progression leading to acute coronary syndrome (ACS) is a rather unpredictable phenomenon. Clinicians currently depend on relatively crude risk scores to identify individuals at risk of developing serious cardiovascular events. Conventional risk factors are able to single out only a proportion of those individuals at a high risk of developing fatal cardiac events. The fact that both atherogenesis and atherosclerotic cardiovascular disease progression are directly linked to inflammatory mechanisms has generated interest among scientists as to the potential role of inflammatory molecules as markers of cardiovascular risk. C-reactive protein, a marker of inflammation, has been shown to add value to the predictive ability of conventional risk factors. However, given the complexity of the mechanisms responsible for both disease progression and acute events, it is unlikely that a single molecule can provide clinicians with an accurate prediction of cardiovascular risk. Current markers, including C-reactive protein, are non-specific and the search should continue for better markers of both atheromatous plaque activity and patient vulnerability. New markers of CAD progression have been identified in recent years, among which, pregnancy-associated plasma protein-A (PAPP-A) appears to offer an interesting profile. Studies have shown that increased levels of PAPP-A in atherogenesis and the prediction of cardiovascular disease progression have been identified in recent years, among which, pregnancy-associated plasma protein-A (PAPP-A) appears to offer an interesting profile. Studies have shown that increased plasma PAPP-A levels correlate with the presence of vulnerable coronary artery stenoses and the extent of angiographic CAD and predict clinical outcome in patients with chronic stable angina by A.A. Elesber et al., on page 1678.

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with multi-vessel disease than in those with single-vessel disease and patients without obstructive CAD. Furthermore, in patients presenting with ACS, PAPP-A has been shown to be a marker for future events.²,³

Extending these findings, Elesber et al.⁶ showed that in patients with chronic stable CAD, increased plasma PAPP-A concentration is a predictor of all-cause mortality. In this study, the prognostic value of PAPP-A was independent of conventional coronary artery atherosclerosis risk factors, extent of CAD, and ejection fraction. Moreover, the prognostic link between plasma PAPP-A levels and the occurrence of death and recurrent ACS was significant even after correcting for the extent of atherosclerosis, one of the most important prognostic factors for stable CAD patients. These findings are of interest as PAPP-A appears to contribute information which is independent and complementary to that afforded by conventional risk markers and markers of inflammation. However, the Elesber study⁶ has limitations, which include, among others: (i) a relatively small and highly selected patient population; (ii) outcome data based, at least partially, on outside medical records; (iii) a lack of information regarding the source of PAPP-A detected in the circulation; and (iv) a lack of data on the relationship between PAPP-A and vulnerable plaques.

As acknowledged by the authors, the fact that their patients represent a selected group could limit the direct application of the study findings to patients seen in current clinical practice. Therefore, further studies in larger, unselected groups of patients are needed to clarify the issue. Similarly, outcome data based on both hospital and outside records, as assessed in this study, may be problematic. However, the effects of this limitation may be attenuated by the availability of data on the majority of the patients over long-term follow-up. Of interest, patients with a higher PAPP-A level in the Elesber study were significantly older and more likely to be hypertensive when compared with patients with lower PAPP-A values, which may suggest that elevations of PAPP-A could be linked to the presence of risk factors and not necessarily to plaque vulnerability. However, PAPP-A was still found to be an independent predictor of future cardiovascular events after correction for conventional cardiovascular risk factors.⁶

The relationship between circulating PAPP-A concentrations and vulnerable plaques was not assessed in the Elesber trial,⁶ but this issue had been tackled previously by Cosinsales et al.² who showed a link between the presence and number of vulnerable plaques and increased PAPP-A levels in patients with stable angina.

Despite these limitations, the study by Elesber et al.⁶ is of importance, as it expands previous observations in angina patients that PAPP-A may be a good, non-invasive marker of risk.

**Problems with current PAPP-A assays**

Although PAPP-A shows some promise as a marker for cardiovascular disease progression, its measurement does present some problems using existing assays. In the circulation, the PAPPA molecule normally exists as a complex with its endogenous inhibitor proMBP, as mentioned previously in this editorial. This complex is found at low levels in normal individuals and high levels during pregnancy.

Recently, Qin et al.¹⁰,¹¹ have shown that atheromatous plaques contain non-complexed PAPP-A and that elevated concentrations of the same form are found in plasma. Importantly, they also showed that antibodies raised against the complexed form do not interact with the non-complexed form.

Bayes-Genis et al.¹ were the first to show that unstable plaques contained PAPP-A and that patients with CAD had elevated serum concentration of PAPP-A. However, their assay, which is similar to that used by Elesber et al.,⁶ was based on antibodies that may or may not have been raised against the non-complexed form of PAPP-A, as the authors did not specify this matter. This assay has never been made available commercially. In addition, the standard material against which the assay was calibrated was WHO reference standard 78/610 which was derived from serum collected from pregnant women. Although this material is for use in assays to determine PAPP-A in plasma from patients with CAD is a contentious issue.

Although sensitive commercial assays, based on a variety of detection antibodies, are now available to measure PAPP-A, they too have been calibrated against material on the basis of complexed PAPP-A found in pregnant women. Although the available data suggest that these assays are capable of associating measured concentrations of PAPPA with cardiovascular events and extent and complexity of coronary atherosclerosis, it would be better if the assays used to investigate any relationship were calibrated against the analyte of interest.

**Future directions**

The confirmatory findings of the Elesber study⁶ are likely to stimulate the search for answers to several questions raised by recent studies regarding the role of PAPP-A in cardiovascular disease. Among the questions awaiting an answer are the following. (i) What is the exact link between PAPP-A and plaque vulnerability? (ii) Is PAPP-A a pathogenic candidate in atherosclerosis? (iii) Is PAPP-A a marker of plaque remodelling rather than plaque disruption? (iv) What is the exact contribution that this marker of cardiovascular risk could make in the clinical setting, in addition to that of conventional markers and C-reactive protein measurements?

In addition, there is a need for assays to be developed that selectively detect the non-complexed form of PAPP-A, at the relatively low concentrations found in the circulation of patients with CAD and that are calibrated using a defined standard of the non-complexed form. Such assays should also have a lower limit of quantification which is appropriate for use with samples from this patient group.

Notwithstanding these uncertainties, the growing body of evidence regarding the potential role of PAPP-A as a predictor of cardiovascular risk should encourage further research in this field.

**Conflict of interest:** none declared.

**References**

Clinical vignette
doi:10.1093/eurheartj/ehi699
Online publish-ahead-of-print 25 January 2006

Cardiac sarcoidosis detected with magnetic resonance imaging

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A 47-year-old woman was admitted for multiple episodes of symptomatic sustained polymorphic ventricular tachycardia. Six weeks earlier, she had been diagnosed of active sarcoidosis (lymph node biopsy demonstrating non-caseating granulomas). A coronary angiogram revealed normal arteries. A cardiac magnetic resonance examination demonstrated severe left ventricular dysfunction (ejection fraction of 27%). Delayed hyperenhancement imaging showed multiple foci of contrast accumulation corresponding to fibrotic and/or inflammatory tissue in the left ventricular wall, predominantly in the intramyocardial and subepicardial layers (Panel A, four-chamber view; Panel B, two chamber view; Panel C, basal short-axis view). Transmural scarring and thinning of the basal septum, a common finding in cardiac sarcoidosis, was also noted (Panels A and C). An endomyocardial biopsy revealed areas of focal fibrosis (asterisk in Panel D) that could explain the magnetic resonance imaging findings, multiple histiocytes (also noted in Panel D), and no evidence of myocarditis or myocyte necrosis. An automatic internal defibrillator was implanted.

Although clinical evidence of myocardial involvement, a leading cause of death in subjects with sarcoidosis, occurs in only 5% of patients, pathological evidence is found in up to 50% of the subjects. Magnetic resonance imaging can non-invasively depict this abnormality.