Expert Review of Cardiovascular Therapy

ISSN: 1477-9072 (Print) 1744-8344 (Online) Journal homepage: informahealthcare.com/journals/ierk20

Elevated PAPP-A sets alarm bells ringing in patients with cardiac chest pain

Goran Loncar & Stephan von Haehling

To cite this article: Goran Loncar & Stephan von Haehling (2014) Elevated PAPP-A sets alarm bells ringing in patients with cardiac chest pain, Expert Review of Cardiovascular Therapy, 12:1, 5-8, DOI: 10.1586/14779072.2013.836966

To link to this article: https://doi.org/10.1586/14779072.2013.836966

Published online: 10 Dec 2013.

Elevated PAPP-A sets alarm bells ringing in patients with cardiac chest pain

Expert Rev. Cardiovasc. Ther. 12(1), 5–8 (2014)

Goran Loncar

Cardiology Department, Zvezdara University Medical Center, Belgrade, Serbia

Stephan von Haehling

Author for correspondence: Department of Cardiology, Charité Medical School, Applied Cachexia Research, Campus Virchow-Klinikum, Berlin, Germany
Tel.: +49 30 450 553506
Fax: +49 30 450 7553506
stephan.von.haehling@web.de

Novel biochemical markers may improve the estimation of overall risk in subjects at a high risk of adverse cardiac events. Measurement of some of these markers, including pregnancy-associated plasma protein A (PAPP-A), brings significant prognostic information independent of traditional risk factors. PAPP-A has been recently identified as a marker of plaque destabilization with growing interest in cardiovascular research. Our group has recently demonstrated that higher levels of serum PAPP-A were independently associated with an increased short-term risk of cardiovascular events in a large sample of 2568 consecutive patients presenting with cardiac chest pain. PAPP-A levels above 34.6 mIU/l in cardiac chest-pain patients sets alarm bells ringing as a warning for higher risk of short-term cardiovascular adverse events, including stent thrombosis, myocardial infarction, ischemic stroke or cardiovascular-related death within 90 days, the combined primary end point of this study. Cardiac chest pain patients with PAPP-A levels above 34.6 mIU/l may suffer from adverse cardiovascular events five times more frequently within 90 days than those with lower PAPP-A levels (hazard ratio: 5.28; 95% CI: 3.81–7.31). However, current data do not support the diagnostic role of PAPP-A for acute coronary syndrome in comparison to the gold standard biomarker troponin. Additionally, PAPP-A is known to interact with heparin, which may diminish its potential utility in every day clinical life. Future multicenter and large-volume studies are warranted to validate the use of PAPP-A in routine clinical practice.

Biomarkers & chest pain

Chest pain patients represent an important population in emergency departments worldwide. Many of them present with suspected acute coronary syndrome (ACS) that is among the leading causes of death in developed countries [1]. Some cardiac biomarkers, such as the troponins, have improved the ability to reveal cardiac injury and, thanks to the high sensitivity and specificity of this biomarker, it is now considered a 'gold standard' in the diagnosis of acute myocardial infarction [2]. However, chest pain patients with normal values of troponin are not necessarily risk free for major cardiovascular events. Some novel biochemical markers may improve the estimation of the overall risk in subjects at a high risk of adverse cardiac events. Such tools include the newly developed biochemical markers upstream of detectable mediators of necrosis, particularly including biochemical markers of plaque destabilization and rupture, C-reactive protein, markers of myocardial stretch (e.g., natriuretic peptides), cellular adhesion molecules and possibly markers of stress [3–6].

Plaque destabilization & PAPP-A

Chronic inflammation is a major feature of atherosclerosis present in the vessel wall throughout all stages of the disease until the final pathophysiological steps, plaque destabilization and eventually plaque rupture, take place with potentially deadly consequences [6]. Previous pathological studies have shown the abundant presence of inflammatory cells such as macrophages and T lymphocytes at the site of plaque rupture. These cells are able to produce various cytokines, growth factors, chemokines, disintegrines that induce activation and proliferation of smooth muscle cells, lesion

Keywords: acute coronary syndrome • chest pain • PAPP-A • unstable plaque

 10.1586/14779072.2013.836966 ISSN 1477-9072

progression and finally weakening of a vulnerable plaque by matrix degradation of its fibrous cap [7]. However, atherosclerosis is not only characterized by a local inflammatory response. Prospective studies have recently shown that several markers of plaque destabilization may be used for prediction of future cardiovascular events not only in patients with ACS, but also in healthy subjects [8]. Importantly, measurement of some of these markers including pregnancy-associated plasma protein A (PAPP-A) brings significant prognostic information, independent of traditional risk factors. PAPP-A has recently been identified as a marker of plaque destabilization with growing interest in cardiovascular research [9] even though some groups failed to identify PAPP-A in the atherosclerotic plaque [10]. These mixed results have led authors to conclude that PAPP-A in ACS may be derived from a site different than ischemic cardiac tissue or the adjacent plaque.

PAPP-A is a high-molecular mass, zinc-binding matrix metalloproteinase, which may be produced by different activated cells in unstable plaques and released in extracellular matrix [9]. Using specific assays, PAPP-A was found to be abundantly expressed in both eroded and ruptured coronary plaques, mainly in monocyte/macrophages present in the cap and shoulder region but was only minimally expressed in stable plaque [9]. PAPP-A is a specific activator of insulin-like growth factor -1 (IGF-1) and acts by degrading IGF-binding proteins-4 and -5, thus allowing active IGF-1 to bind to cell surface type 1 IGF receptors [11]. IGF-1 promotes cell proliferation, differentiation, migration, inflammatory cell activation, LDL-cholesterol uptake and release of inflammatory cytokines, thus contributing to plaque progression and destabilization. Whether PAPP-A can directly dissolve extracellular matrix remains unclear [9]. Thus, several previous studies showed that PAPP-A levels are a mediator of adverse inflammatory events, but it has also been proposed that PAPP-A may be a suppressor rather than a mediator of inflammation and tissue damage [12].

PAPP-A & cardiac chest pain

Our group has recently demonstrated that higher levels of serum PAPP-A were independently associated with an increased short-term risk of cardiovascular events in a large sample of 2,568 consecutive patients presenting with cardiac chest pain [13]. This study is by far the largest so far in which blood samples for PAPP-A were taken from patients with cardiac chest pain. PAPP-A levels above 34.6 mIU/l in cardiac chest pain patients set alarm bells ringing as a warning for higher risk of short-term cardiovascular adverse events including stent thrombosis, myocardial infarction, ischemic stroke or cardiovascular-related death within 90 days, the combined primary endpoint of this study. Cardiac chest pain patients with PAPP-A levels above 34.6 mIU/l may suffer from adverse cardiovascular events five-times more frequently within 90 days than those with lower PAPP-A levels (hazard ratio: 5.28; 95% CI: 3.81–7.31). This study also showed higher levels of PAPP-A in patients with ACS than in those with stable angina; however, risk prediction was similarly effective in the two groups. Even more important, male and female patients did not present different serum values of PAPP-A even though the name suggests an association with pregnancy. However, although PAPP-A has long been used in the screening of fetal trisomy, the peptide's name is misleading and it may be time to re-name the peptide to plaque-associated plasma protein A for certain indications.

These findings support the results of earlier studies that suggested PAPP-A as a marker of plaque instability, the first of which was published in 2001 [9]. Several previous studies have investigated PAPP-A as a potential marker of risk for clinical complications. Iversen and colleagues showed that PAPP-A was an independent predictor of mortality in both patients with high-risk non-ST-elevation ACS (NSTE-ACS) and those with ST-elevation myocardial infarction (STEMI) during a median follow-up time of 3 years [14]. Patients in the higher quartiles had a greater risk of death in both NSTE-ACS and STEMI group. Additionally, in STEMI patients in the highest quartile (PPAP-A >35.8 mIU/l), the effect was even stronger compared with the pooled three lower quartiles. Obviously, this predictive value was similar to the one detected as optimal cutoff point of PAPP-A in the recent study of our group, even though a note of caution is warranted, because different assay kits may not be easily interconvertible.

In a study by Cosin-Sales and colleagues, patients with stable angina who had complex angiographic stenosis morphology, had higher serum PAPP-A levels than those who did not [15]. Additionally, PAPP-A was prospectively associated with future death and ACS in such patients [16]. Heeschen and colleagues found that PAPP-A (optimal cutoff 12.1 mIU/l) was an independent predictor of death and myocardial infarction in both troponin-positive and -negative patients [17]. The difference between the optimal cutoff value in the study of von Haehling and the one calculated by Heeschen and colleagues are probably due to the difference in assays and length of follow-up periods. Similar to our study, several studies have consistently shown higher PAPP-A levels in patients with ACS or multivessel coronary artery disease than in patients with stable angina or single-vessel disease [18]. Current data do not support the diagnostic role of PAPP-A for ACS in comparison to the gold standard biomarker troponin [19]. Additionally, one recent study showed that PAPP-A lost its predictive value for adverse clinical outcome in chest pain patients with clinically suspected ACS after correction for confounding factors [20].

PAPP-A as potential cardiovascular marker

Development of biomarkers whose circulating levels suggest that the status of plaque instability seems to be of particular value in prognosis and risk stratification [21]. Higher levels of serum PAPP-A were independently associated with an increased risk of cardiovascular events in patients with cardiac chest pain as demonstrated in several recent studies. Several factors need to be fulfilled for nomination of biochemical substance as a cardiac biomarker such as biological plausibility, the availability

at reasonable cost, rapid and high-quality assays (accurate, reproducible, standardized), the correct interpretation by clinicians using optimal cutoff and optimal time of assessment, and finally, an advantage over currently available tools. Among others, not all assays developed for the detection of PAPP-A in prenatal screening may be suitable for use in patients with coronary artery disease [22]. Thus, the crossing from bench to bedside for PAPP-A must be associated with development of routine assays with standardized and fast procedure of measurement at reasonable cost with interpretative reporting tests. Unlike to the validated clinical utility of PAPP-A in the screening for fetal trisomy [23], its clinical role in coronary artery disease is still not clear. Additionally, PAPP-A is known to interact with heparin [24]. Thus, administration of heparin disables the assessment of PAPP-A in patients with acute chest pain and diminishes its potential utility in the acute clinical setting; however, later analyses in the course of the disease may still have clinical merit. Future multicenter and large volume studies are warranted to validate the use of PAPP-A in routine clinical practice. If these studies confirm the value of PAPP-A, it may become a new cardiovascular marker with an important role in the management of coronary artery disease.

Financial & competing interests disclosure

G Loncar declares no conflict of interest. S von Haehling has been a paid consultant to Thermo Fisher Scientific, Solartium Dietetics, Professional Dietetics, Pfizer, Respicardia and Vifor Pharma; he has received payment from the Heart Failure Association of the European Society of Cardiology to develop educational presentations and travel support from Novartis Pharma; his institution has received a research grant from Vifor Pharma.

References

1 Anderson JL, Adams CD, Antman EM *et al.* ACC/AHA guidelines for the management of patients with unstable angina/non–STelevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients with Unstable Angina/Non–ST-Elevation myocardial infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J. Am. Coll. Cardiol.* 50, e1–e157 (2007).

2 Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined: a consensus document of The Joint European society of cardiology/American College of cardiology committee for redefinition of myocardial infarction. *J. Am. Coll. Cardiol.* 36, 959–69 (2000).

3 von Haehling S, Papassotiriou J, Hartmann O *et al.* Mid-regional pro-atrial natriuretic peptide as a prognostic marker for all-cause mortality in patients with symptomatic coronary artery disease. *Clin. Sci. (Lond.)* 123, 601–610 (2012).

4 von Haehling S, Jankowska EA, Morgenthaler NG *et al.* Comparison of midregional pro-atrial natriuretic peptide with N-terminal pro-B-type natriuretic peptide in predicting survival in patients with chronic heart failure. *J. Am. Coll. Cardiol.* 50, 1973–1980 (2007).

5 von Haehling S, Papassotiriou J, Morgenthaler NG *et al.* Copeptin as a prognostic factor for major adverse cardiovascular events in patients with coronary artery disease. *Int. J. Cardiol.* 162, 27–32 (2012).

6 Koenig W, Khuseyinova N. Biomarkers of atherosclerotic plaque instability and rupture. *Arterioscler. Thromb. Vasc. Biol.* 27, 15–26 (2007).

7 Shah PK. Mechanisms of plaque vulnerability and rupture. *J. Am. Coll. Cardiol.* 41, 15S–22S (2003).

8 Stary HC, Chandler AB, Dinsmore RE *et al.* A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation* 92, 1355–1374 (1995).

9 Bayes-Genis A, Conover CA, Overgaard MT *et al.* Pregnancy associated plasma protein A as a marker of acute coronary syndromes. *N. Engl. J. Med.* 345, 1022–1029 (2001).

10 Iversen K, Teisner A, Dalager S, Olsen KE, Floridon C, Teisner B. Pregnancy-associated plasma protein-A (PAPP-A) is not a marker of the vulnerable atherosclerotic plaque. *Clin. Biochem.* 44, 312–318 (2011).

11 Bunn RC, Fowlkes JL. Insulin-like growth factor binding protein proteolysis. *Trends Endocrinol. Metab.* 14, 176–181 (2003).

12 Conti E, Andreotti F, Zuppi C. Pregnancy-associated plasma protein a as predictor of outcome in patients with suspected acute coronary syndromes. *Circulation* 109, e211–e212 (2004).

13 von Haehling S, Doehner W, Jankowska EA *et al.* Value of serum pregnancy-associated plasma protein A for predicting cardiovascular events among patients presenting with cardiac chest pain. *CMAJ* 185, E295–E303 (2013).

14 Iversen KK, Dalsgaard M, Teisner AS *et al.* Usefulness of pregnancy-associated plasma protein A in patients with acute coronary syndrome. *Am. J. Cardiol.* 104, 1465–1471 (2009).

15 Cosin-Sales J, Christiansen M, Kaminski P *et al.* Pregnancy associated plasma protein A and its endogenous inhibitor, the proform of eosinophil major basic protein (proMBP), are related to complex stenosis morphology in patients with stable angina pectoris. *Circulation* 109, 1724–1728 (2004).

16 Elesber AA, Conover CA, Denktas AE *et al.* Prognostic value of circulating pregnancy-associated plasma protein levels in patients with chronic stable angina. *Eur. Heart J.* 27, 1678–1684 (2006).

17 Heeschen C, Dimmeler S, Hamm CW *et al.* CAPTURE Study Investigators. Pregnancy-associated plasma protein-A levels in patients with acute coronary syndromes: comparison with markers of systemic inflammation, platelet activation, and myocardial necrosis. *J. Am. Coll. Cardiol.* 45, 229–237 (2005).

18 Cosin-Sales J, Kaski JC, Christiansen M *et al.* Relationship among pregnancy associated plasma protein-A levels, clinical characteristics, and coronary artery disease extent in patients with chronic stable angina pectoris. *Eur. Heart J.* 26, 2093–2098 (2005).

19 Schaub N, Reichlin T, Meune C *et al.* Markers of plaque instability in the early diagnosis and risk stratification of acute myocardial infarction. *Clin. Chem.* 58, 246–256 (2012).

20 Mjelva OR, Brügger-Andersen T, Pönitz V *et al.* Long-term prognostic utility of PAPP-A and calprotectin in suspected acute coronary syndrome. *Scand. Cardiovasc. J.* 47, 88–97 (2013).

21 Zaninotto M, Mion MM, Novello E, Altinier S, Plebani M. New biochemical markers: from bench to bedside. *Clin. Chim. Acta*. 381, 14–20 (2007).

22 Qin QP, Kokkala S, Lund J *et al.* Immunoassays developed for pregnancy-associated plasma protein-A (PAPP-A) in pregnancy may not recognize PAPP-A in acute coronary syndromes. *Clin. Chem*. 52, 398–404 (2006).

23 Barrett SL, Bower C, Hadlow NC. Use of the combined first trimester screen result and low PAPP-A to predict risk of adverse fetal outcomes. *Prenat. Diagn*. 28, 28–35 (2008).

24 Hájek P, Macek M Sr, Lashkevich A *et al.* Influence of concomitant heparin administration on pregnancy-associated plasma protein-A levels in acute coronary syndrome with ST segment elevation. *Arch. Med. Sci*. 7, 977–983 (2011).