

## COPEPTIN – IS THERE A ROLE FOR ANOTHER CARDIAC BIOMARKER?

### KOPEPTIN – POSTOJI LI ULOGA ZA NOVI SRČANI BIOMARKER?

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**Summary:** The discovery and development of new biomarkers continues to be a promising field. Since cardiovascular disease remains the principal cause of death in the developed countries, this is the area in which novel biomarkers have been most extensively evaluated. Arginine vasopressin (AVP or antidiuretic hormone) is one of the key hormones in the human body involved in cardiovascular homeostasis. It has so far escaped introduction into the routine clinical laboratory due to technical difficulties and pre-analytical errors. Copeptin, the C-terminal part of the AVP precursor peptide, was found to be a stable and sensitive surrogate marker for AVP release. During the past years, copeptin measurement has been shown to be of interest in a variety of clinical indications, including cardiovascular diseases such as heart failure, myocardial infarction, and stroke. This review summarizes the recent progress in the diagnostic use of plasma copeptin in cardiovascular diseases.

**Keywords:** biomarker, copeptin, heart failure, myocardial infarction

**Kratak sadržaj:** Otkriće i razvoj novih biomarkera je područje koje u posljednje dve decenije beleži značajan napredak i zauzima važno mesto na polju kliničke medicine. Kako kardiovaskularne bolesti i dalje predstavljaju glavni uzrok morbiditeta i mortaliteta u razvijenim zemljama, upravo je na tom polju evaluacija novih biomarkera najopsežnija. Arginin-vazopresin (AVP ili antidiuretski hormon) jedan je od ključnih hormona uključenih u održavanje homeostaze u kardiovaskularnom sistemu. Do danas je njegovo određivanje u rutinskoj laboratorijskoj dijagnostici ostalo problematično usled tehničkih poteškoća, ali i brojnih preanalitičkih grešaka. Kopeptin, C-terminalni deo prekursora AVP, stabilan je i osjetljiv surogat marker otpuštanja AVP-a. Poslednjih godina, određivanje koncentracije kopeptina dalo je značajan doprinos u dijagnostici i prognozi različitih oboljenja, uključujući i kardiovaskularne bolesti, kao što su srčana slabost, infarkt miokarda i moždani udar. Ovaj pregledni članak prikazuje dosadašnji napredak u dijagnostici i prognozi kardiovaskularnih bolesti zahvaljujući određivanju koncentracije kopeptina kao novog biomarkera.

**Ključne reči:** biomarker, kopeptin, srčana slabost, infarkt miokarda

### Introduction

The discovery and study of novel biomarkers represent the most extensively developing areas of clinical chemistry and clinical medicine in the last two decades and continue to be an exciting and promising field (1). Apart from oncology, cardiovascular di-

seases are the field in which novel biomarkers have been most extensively evaluated. Improvement in knowledge of the pathophysiology of atherosclerosis has allowed the discovery and development of many markers associated with myocardial ischemia. Biomarkers have become increasingly important in this setting to supplement electrocardiographic findings and patient history because one or both can be misleading (2). A multimarker approach incorporating biomarkers and clinical scores will increase the diagnostic and prognostic accuracy. However, only a minority of the investigated markers have demonstrated a significant diagnostic and/or therapeutic impact (3). Assessment of the clinical potential of a novel

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biomarker may be structured around three fundamental questions: A) Can the laboratory measure it accurately and in a timely manner? B) Does it add new information? C) Does it help the clinician to manage patients? (4). This review will discuss copeptin, a new biomarker candidate for diagnosis and risk stratification in patients with acute coronary syndrome which might meet all of these criteria.

### The stress hormone copeptin

Stress is defined as anything that throws the body out of homeostatic balance. A sign of the stress response is the activation of the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis. The hormonal cascade, initiated by a stressor through the brain stem and limbic pathways, involves the release of corticotropin-releasing hormone (CRH) from parvocellular neurons in the paraventricular nucleus of the hypothalamus. CRH stimulates the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland. Another hypothalamic hormone which is stimulated by different stressors is vasopressin (AVP). AVP, also termed antidiuretic hormone, seems to exert a potentiating action on CRH, thus these two agents together are considered the main secretagogues of ACTH. ACTH, in turn, stimulates the adrenal cortex to produce cortisol. Many factors influence the pattern and magnitude of the response to a stressor, including the duration of the stressor exposure (acute versus chronic), the type of stressor (physical versus psychological), the stress context, age and gender (5–8).

The AVP system plays a crucial role in the regulation of the individual endogenous stress response (8). AVP is a nonapeptide produced in the hypothalamus and is released from the neurohypophysis into the blood to induce water conservation by the kidney, contributing to the regulation of osmotic and cardiovascular homeostasis (9). AVP is derived from a larger precursor (pre-provasopressin) along with two other peptides, neurophysin II and copeptin (10). Neurophysin II has a complex structure with many putative intramolecular disulfide bonds, and it may be associated with AVP during maturation and transport. Copeptin, the C-terminal part of provasopressin, is a 39 amino acid glycopeptide of unknown function (9). Copeptin may have a role during the intracellular processing of provasopressin, possibly contributing to the correct structural formation of the precursor, which leads to efficient proteolytic maturation (9). Levels of AVP have been shown to be elevated in heart failure (2–4, 11, 12) and in different states of stress (8), but investigation of the AVP system has been limited so far because AVP is highly unstable (plasma half-life: 5 to 15 minutes) and largely attached to platelets (4). Copeptin is secreted stoichiometrically with AVP by the neurohypophysis and is much more stable, thus overcoming the limitations and difficulties of assess-

ing the AVP system (12). In the past two years copeptin has been studied as a diagnostic and as a prognostic marker in different diseases associated with stress.

As a diagnostic marker, copeptin was evaluated in patients with diabetes insipidus after pituitary surgery. In these patients, copeptin had superior diagnostic accuracy to detect the insufficient activity of the posterior pituitary, offering an alternative to the laborious and ambiguous water-deprivation test (13). As a prognostic marker, copeptin levels were independent predictors of survival in critically ill patients suffering from hemorrhagic and septic shock. Recent studies showed that copeptin was elevated in patients with sepsis and septic shock due to an insufficient hemodynamic response and due to the activation of the HPA axis (8, 14). According to those studies, copeptin levels were also significantly higher in patients with lower respiratory tract infections compared to healthy controls, with the highest levels in patients with community acquired pneumonia (CAP). Copeptin levels increased with increasing severity of CAP, as defined by the gold standard pneumonia severity index. In patients who died, copeptin levels on admission were significantly higher compared to the levels measured in survivors. These facts indicate that copeptin could be a valuable novel prognostic biomarker in lower respiratory tract infections including pneumonia (15, 16). One prospective, observational study evaluated copeptin as a novel, strong and independent prognostic marker for functional outcome and death in patients with ischemic stroke. According to that study, copeptin may also contribute to improved risk stratification and allocation of targeted therapies for stroke patients and other acute illnesses in the future (17–19).

Previous study data demonstrated that copeptin levels increase progressively with the severity of sepsis and are independent predictors of mortality in ventilator-associated pneumonia (VAP) (10). According to Jochberger et al, copeptin plasma concentrations were significantly higher in critically ill patients, compared to healthy volunteers (20). Cardiac surgery patients had higher copeptin plasma concentrations than critically ill patients with sepsis and with SIRS. In healthy volunteers as well as in critically ill patients, plasma concentrations of AVP and copeptin correlate significantly with each other. Although the ratio of copeptin/AVP plasma concentrations was comparable in healthy volunteers and patients after cardiac surgery, it was significantly increased in critically ill patients with sepsis and with SIRS (20).

### Copeptin as a novel biomarker in cardiovascular diseases

Today, cardiac troponins (I and T) represent clinical laboratory standards due to their myocardial tissue specificity and sensitivity in diagnosing acute

myocardial infarction (AMI) and in the risk-stratification of patients with acute coronary syndromes (ACS). The major limitation of current troponin assays is the probability of normal levels in AMI patients at presentation, due to a possibly delayed increase in plasma concentration. Exclusion of AMI consequently requires prolonged monitoring over 6 to 9 h and serial blood sampling (2, 3). Other non-myocardial tissue-specific markers might be of help in this setting. According to data from recent studies, the combination of troponin and copeptin allows a rapid and reliable rule out of AMI right at the initial blood draw when the patient presents to the Emergency Department (ED) (21). With the high sensitivity troponins, diagnostic sensitivity has been increased at the expense of specificity. For this reason, it makes sense to combine copeptin even with high sensitivity troponins. The cut-off for copeptin was determined in such a way as to achieve maximal safety for ruling out AMI. At a comparable level of sensitivity, specificity is just 70% when using only high sensitivity troponins. (2)

The outcome of AMI has improved with advances in medical therapy, but heart failure (HF) remains a leading cause of cardiovascular morbidity and mortality, after AMI. Clinical features may be useful for predicting which patients might be at risk of developing these complications after AMI, but they lack sensitivity and specificity. Biomarkers are emerging as a useful tool for predicting prognosis in such patients (12, 22). B-type natriuretic peptide and its more stable counterpart, N-terminal pro-B-type natriuretic peptide (NTproBNP), have shown great promise in this area, covering a range of acute coronary syndromes. Novel biomarkers are emerging that may also be of use. Recent research has demonstrated that copeptin may predict adverse outcome, especially in those with elevated NTproBNP (12, 22, 23). In patients with destabilized heart failure, copeptin was an accurate prognostic marker for mortality. In post-acute myocardial infarction cases, copeptin was elevated in patients who died compared with survivors. Copeptin was thereby a significant independent predictor of death or heart failure within 60 days (12, 13, 23, 24).

### Copeptin plasma levels in patients after cardiac surgery

All surgical treatments are followed by a period of heart ischemia and could be associated with AMI. The diagnosis of postoperative AMI is very important because it can be associated with significant cardiovascular morbidity and mortality. Troponins T and I constitute the 'gold standard' for the detection of myocardial necrosis and risk stratification, but even current fourth generation troponin assays have certain limitations (2). As no marker has supplanted cardiac troponins, many researchers have advocated multimarker testing (25). Copeptin is a biomarker that can be effective in assessing cardiac function and car-

diac ischemia. After an ischemic event, it appears very early in the circulation, which puts it into the group of early ischemia biomarkers. In combination with other markers and the Euro-SCORE-compatible devices, it might be a predictor of outcome in patients after coronary artery bypass graft surgery (21).

Preliminary results of our study, preformed to evaluate the copeptin plasma levels in patients before and after aortocoronary bypass surgery, have shown low copeptin levels in patients before cardiac surgery (group A), significantly elevated plasma levels of copeptin in patients immediately after cardiac surgery (group B), and a sharp decrease in the plasma levels of copeptin eight hours after surgery (group C).

Troponin T levels were also measured in order to compare copeptin and troponin levels, since troponin is still the biomarker of choice for diagnosing AMI.

The study included 98 (76 male and 22 female) patients with inadequate perfusion of the myocardium undergoing aortocoronary bypass surgery. The study was preformed according to the principles of the Declaration of Helsinki and approved by the hospital Ethics Committee. Written informed consent was obtained from all participating patients.

Copeptin plasma levels were measured without prior extraction using a commercial EIA kit (Phoenix Pharmaceuticals, Inc., SAD). Troponin T levels were determined by the Roche Elecsys 2010 electrochemoluminescence assay according to the manufacturer's instructions (Roche Diagnostics GmbH, Mannheim, Germany).

Kolmogorov-Smirnov test was used to test the normal distribution of numerical data.

Repeated measures ANOVA was used for data comparison, and only  $p < 0.05$  was considered statistically significant. Correlation of copeptin and troponin T levels was also preformed and the Spearman correlation coefficient was calculated. MedCalc 9.2.0.0 statistical software (MedCalc, Mariakerke, Belgium) was used for statistical analysis. Values of copeptin and troponin T for each group are shown in Table I.

**Table I** Copeptin and troponin T plasma levels (mean  $\pm$  SD) in patients before, immediately after and eight hours after cardiac surgery.

	Group A	Group B	Group C	P
N	98	98	98	/
Troponin T, ng/mL (mean $\pm$ SD)	0.05 $\pm$ 0.13	0.64 $\pm$ 1.19	1.18 $\pm$ 1.25	< 0.001
Copeptin, ng/mL (mean $\pm$ SD)	0.91 $\pm$ 0.42	1.45 $\pm$ 0.46	0.49 $\pm$ 0.35	< 0.001

SD – standard deviation

Correlation coefficients of copeptin and troponin T for groups A, B and C were as follows:  $r_A = -0.03$ ,  $r_B = 0.11$  and  $r_C = 0.16$ .

Copeptin levels were significantly elevated immediately after cardiac surgery, and sharply decreased eight hours after the intervention, while troponin T levels showed maximal increase eight hours after surgery, suggesting that copeptin could be an early marker of myocardial ischemia. Low correlation coefficients show that there was no correlation between the plasma levels of troponin and copeptin in the examined patients, and indicate that copeptin is an independent factor of possible myocardial ischemia. However, it is necessary to expand this research to a larger scale of patients following post-surgical outcome in order to be able to define the clinical value of copeptin as a biomarker in predicting the outcome of patients after coronary bypass surgery.

According to the described facts, a few questions remain that need to be answered.

1) *Why is copeptin a good prognostic tool in a variety of diseases?*

Vasopressin, together with CRH, is the main secretagogue of the HPA axis that stimulates the secretion of ACTH and cortisol. Serum cortisol levels are known to be in proportion to the degree of stress and, by mirroring the individual stress level, to predict outcome in sepsis and pneumonia (26). Importantly, copeptin levels seem to mirror even more subtly moderate levels of stress than cortisol levels. (27)

Copeptin analysis may be suitable to answer vital clinical questions. For the critical care clinician, this could be particularly helpful in patients where knowledge of endogenous vasopressin, mirrored by copeptin concentrations, is crucial for therapy (28), such as in patients with prolonged hypotension and ongoing vasopressor drug requirements or in patients with electrolyte disturbances (29).

2) *Is there a role for another cardiac biomarker?*

Due to the limitations of current troponin assays, the diagnosis of AMI cannot be excluded in a large proportion of patients at the time of presentation, which can lead to costly evaluation and prolonged hospital stay until AMI can definitively be ruled out. On the other hand, usage of those assays results in 1–2% of patients with AMI who are misdiagnosed and sent home leading to an adverse outcome (2).

The outcome of patients after AMI has improved with the advances in medical therapy, but HF remains a leading cause of morbidity and mortality after AMI. Biomarkers in this field are also emerging as useful tools for predicting prognosis in those patients. NTproBNP and BNP have shown great promise in this area (22). However, heart failure is a complex disease process, and dysfunctions in multiple physiologic processes are involved in its pathogenesis. As a result, a single biomarker is unlikely to be sufficient for risk prediction and therapy guidance. Thus,

a combination of several biomarkers representing different pathophysiological processes may be required in future biomarker-guided therapy trials (22, 23). Finally, one also has to keep in mind that biomarker-guided therapy in heart failure is a nascent field. It has been limited to natriuretic peptides, which are the only well studied biomarkers in heart failure to date. In recent years, significant efforts have been put into the discovery and application of new biomarkers (30).

According to these facts, there is a role for new cardiac biomarkers. There is some evidence that a multi-marker strategy, rather than a single biomarker, can improve the diagnosis, risk stratification and prognosis of patients with cardiovascular disease. The additional use of copeptin seems to allow a rapid and reliable rule out of AMI already at presentation and may thereby obviate the need for prolonged monitoring and serial blood sampling in the majority of patients. This change in clinical practice may provide the opportunity to significantly improve patient management in the ED and to reduce treatment cost (21).

3) *What are the limitations and potentials of copeptin use in cardiovascular diseases?*

Recent studies have demonstrated that copeptin has the potential to become an important diagnostic and prognostic biomarker in cardiovascular disease, especially when the results are combined with current assays used in these patients.

However, as for all other biomarkers, there are also limitations concerning copeptin. First, there is the drug influence. In one study in healthy participants, copeptin was inhibited in a dose dependent way during prednisone treatment, indicating direct corticosteroid influence on copeptin levels. Furthermore, it has been noticed that copeptin levels are higher in patients with renal insufficiency. Knowledge of assay characteristics (sensitivity, strengths, pitfalls and optimal cut-off levels in a predefined clinical setting) are required for its optimal use in clinical practice (8).

## Conclusion

Any biomarker will always oversimplify the interpretation of important variables, and therefore biomarkers are meant to complement, rather than replace, the clinician's judgment and/or validated clinical severity scores. Conceptually, the likelihood of an adverse outcome should determine the medical indication, the length of hospitalization and the allocation of healthcare resources (13). It is time to perform randomized trials using biomarkers such as copeptin in specific settings to guide the allocation of hospital resources, including the need for intensive care admission and duration, in order to ultimately prove their clinical usefulness and cost-efficiency.

## Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.



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*Received: April 15, 2011*

*Accepted: May 25, 2011*