

## DETERMINING BNP AND NT PRO-BNP IN PATIENTS WITH THE ACUTE CORONARY SYNDROME

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Acute coronary syndrome represents a group of different clinical conditions resulting from an acute ischemia or myocardial necrosis caused most frequently by an acute coronary lesion formed by a rupture of atherosclerotic plaque in the coronary artery with a concurrent thrombosis, inflammation, vasoconstriction and micro-embolization.

Acute coronary syndrome can manifest as an unstable angina pectoris, an acute myocardial arrest with or without a ST elevation or as sudden cardiac death.

Determination of heart damage markers in the serum is particularly important to confirm the diagnosis of acute myocardial arrest without a ST elevation. Each increase in cardio specific enzymes signifies myocardial necrosis and meets the conditions for making the diagnosis of an acute myocardial arrest. Larsen et al. tested the importance of BNP, and Bazzino et al. of NT pro-BNP in patients with acute coronary syndrome (ACS). A high level of natriuretic peptides indicated a high risk of cardiac complications.

Our aim was to evaluate the importance of efficient determination of biochemical markers in ACS patients, importance in making the diagnosis, evaluation of treatment depending on the severity of clinical signs, as well as in the stratification of risk for coronary relapse.

The paper is a review of the importance BNP and NT pro-BNP as the new approaches in the diagnosis and treatment of ACS patients.

The goal was to show that the markers of heart function have a role in ACS settings. Furthermore, the study assessed the severity of clinical picture, complications and possible coronary relapses. Further studies will present some more elaborate data on their importance in risk stratification and decision-making in further management of these patients. *Acta Medica Medianae* 2016;55(4):21-27.

**Key words:** Acute Coronary Syndrome, Biochemical Markers, Natriuretic Peptides, BNP, NT pro-BNP

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### Introduction

Biochemical heart markers have an important role in the diagnosis and treatment of ACS patients.

The following three classes of indicators are used: myocyte necrosis markers, inflammation markers and heart function markers. Heart function markers, heart natriuretic peptides are used in the diagnosis and clinical assessment of heart failure.

The field of biochemical markers is a very dynamic one, with constant appearance of new

markers. As a result, recent research has been focused on discovering markers which would be used to monitor the progression and prognosis of the disease, predicting thus complications as well (1, 2).

### Goal

The goal of the study was to evaluate the importance of efficient determination of biochemical markers in ACS patients, their importance in diagnosis, post treatment follow-up depending on the severity of clinical picture, as well as in risk stratification for coronary event relapse.

Natriuretic peptides ANP (atrium natriuretic peptide) and BNP (brain natriuretic peptide) are synthesized in myocardial cells, and have a vasodilation effects, increase sodium diuresis and decrease aldosterone secretion. Within heart cells, pro-BNP (containing 108 amino acids) is synthesized, and further divided into N-terminal pro-BNP (with 76 amino acids) and C-terminal peptide

(with 32 amino acids). Numerous studies have described an increase in the levels of these peptides in ACS patients, and also in patients with heart failure and elevated arterial pressure. Some studies show that changes in their concentration in patient serum can be seen prior to the changes in hemodynamic and echocardiography parameters. Natriuretic peptides were first described 20 years ago. Their name originates from the organ from which they were isolated. Later, it was discovered that the largest amounts of BNP can be found in the heart ventricles. ANP and BNP are circulating hormones with natriuretic, vasodilator, renin-inhibitory and exert antimitogenic effects cardiovascular tissues, they act as system antagonists of the renin-angiotensin-aldosterone system and sympathetic nerve system. They are important regulators of blood pressure and homeostasis of water electrolytes in the body (3).

The family of natriuretic peptides also contains a C-type natriuretic peptide (CNP) and urodilatin. The synthesis of prohormone precursors for each natriuretic peptide is regulated by different genes. All peptides in their structure contain a chain of 17 amino acids with a disulfide bridge between two cysteine remains responsible for the biological activity of natriuretic peptides and their recognition by receptors. The regulation of synthesis and pro-BNP excretion is determined by gene expression. Under pathological conditions, the main source of BNP are the heart chambers.

The extension of the left chamber wall is the primary regulator of BNP emission (4). They are removed from the circulation by means of natriuretic peptide receptor C, NPR-C. They are disintegrated under the influence of a neutral endopeptidase - NEP. ANP, BNP, NT pro-ANT and NT pro-BNP are increased in all edematous irregularities with increased tension in the chamber wall, pre-chamber wall such as a chronic heart failure, renal failure, liver cirrhosis with ascites. ANP and BNP secretion varies depending on whether a pre-chamber distension (in mitral stenosis) or left chamber (in hypertrophic obstructive cardiomyopathy) or both chamber and pre-chamber distension (in dilative cardiomyopathy) is primarily present. Determination of natriuretic peptides has not been standardized, and literature data on the reference values, conditions of determination vary, similar to the results obtained by using immunochemical tests by different manufacturers (3). A blood sample is collected into plastic test tubes with EDTA. The level of natriuretic peptides can be affected by salt from food intake, as well as by medication - glucocorticoids, thyroid hormones, diuretics, ACE inhibitors, beta-blockers, adrenergic agonists. It is also important to control the presence of renal and hepatic diseases because the substances are partly eliminated through the liver and kidney, and in these conditions their excretion is also stimulated by an increase in water content. The concentrations of ANP and BNP in healthy population range from 3-6 pmol/l, with

20-50 times greater values for NT pro-BNP and NT pro-ANP. According to the data, their values tend to rise with advancing age.

## Methods

The study represents a review of the importance of determination of BNP and NT pro-BNP as new methods in the diagnosis and treatment of ACS patients.

Clinical and experimental studies (3, 5, 6, 7) have shown that natriuretic peptides are released by ischemic cardiomyocytes and that hypoxia stimulates the release of these peptides from the myocardium itself. The most severe forms of ischemia can result in a myocardial arrest. An acute myocardial arrest (AMA) is accompanied by a complex neurohormonal activation which involves the renin-angiotensin-aldosterone system (RAAS), sympathetic and increased secretion of arginine vasopressin and adrenal catecholamine within first 2-3 days after the arrest. Natriuretic peptides are increased during the acute phase and probably have a compensatory role. The increase is caused by irregularities in chemodynamics, ischemia, increased synthesis in the peri-arrest zone, and releases from the necrotic myocardium. The peak elevation of BNP and NT pro-BNP values occurs after about 16 hours from the beginning of the arrest, followed by a decrease in these values. In patients with dysfunctional left chamber, the secondary peak is observed in the subacute phase, several days after ACA. A low level of neuro-hormone activation can be seen 1-2 weeks after the arrest if the heart failure is not treated with diuretics. The best prognostic markers of morbidity and mortality have been noticed during the sub-acute phase of AIM. BNP is the only significant, prognostic marker of the cardiovascular mortality.

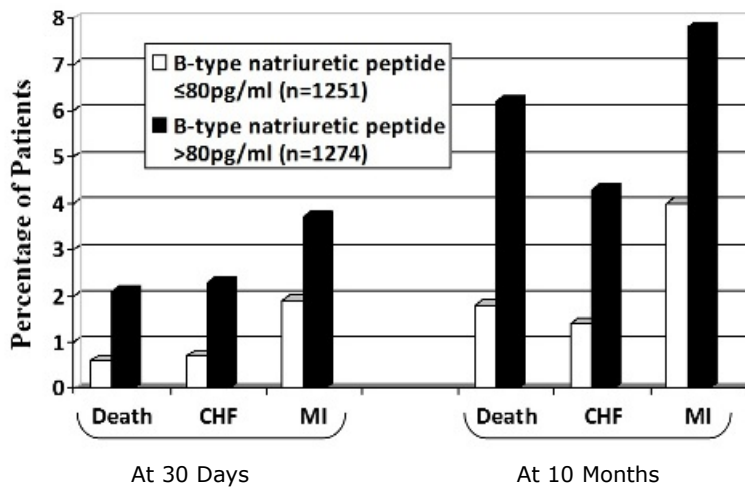
Contemporary research in the field aims at finding some simple monitoring methods, preferably single laboratory assays, to predict the development of specific cardiovascular diseases (CVD) and their complications, and to observe the effectiveness of the applied therapy. Numerous articles describe the importance of determination of NT pro-BNP in patients before the first symptoms appear. It has been reported that there is a correlation between these heart markers and systolic function of the left chamber, while the diastolic function cannot always be correlated with NT pro-BNP. The impact of these markers on the development of heart failure in patients with ACS has also been shown. In 1993 and 1996, three separate studies showed a strong correlation between the BNP level in the acute and sub-acute phase and long term mortality after AMA. The B-type peptides and LVEF were predictors of death, heart failure, and new myocardial infarction. A study by Richards et al. (1998) found a correlation between the level of NT pro-BNP and prognosis after AMA. BNP and NT pro-BNP values in the sub-acute phase were good predictors of long-term

mortality and mortality as a whole, and also for hospital readmission due to heart failure after AMA. The data from two small studies showed that circulating BNP and NT pro-BNP levels were higher in patients with unstable angina pectoris than in patients with stable coronary disease. One study showed a correlation between the BNP level and regional wall mobility impairment, confirmed by echocardiography, which supported the evidence that BNP production is correlated with the severity of coronary disease and myocardial thickness and risk. Recently, it has become known that BNP and NT pro-BNP levels in patients with unstable angina pectoris and NSTEMI correlated significantly with a deadly outcome within 43 days. Lamos et al. studied the prognostic value of BNP in 2525 patients with ACS. A group with an unstable angina pectoris and NSTEMI was also included. The study showed that the level of BNP taken 40±20 hours after the onset of symptoms predicts an increase in thirty-day and ten-month mortality (Graph.1).

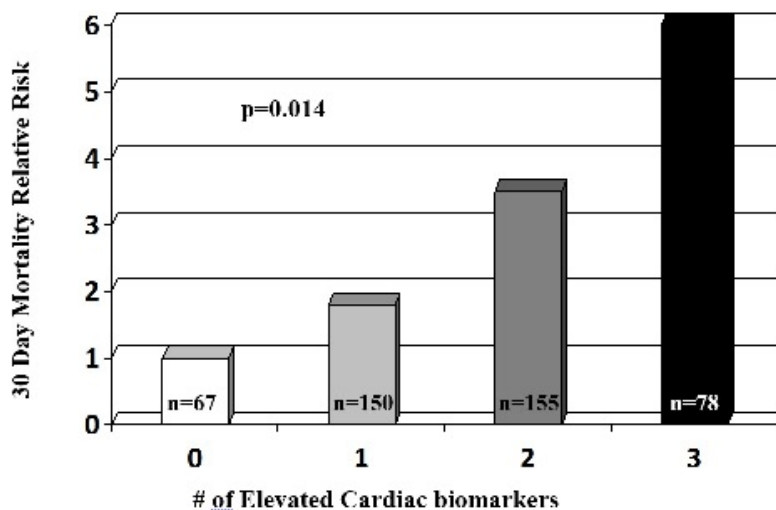
It also found that the predictive ability of survival and re-hospitalization was equally strong in all ACS cases. The study showed for the first time that BNP could predict recurrent ischemic events when the level was above 80 pg/ml.

Mc Donagh et al. (6, 8)) found that BNP was useful in determining heart failure in later studies, and Smith et al. tested the usefulness of BNP in diagnosing systolic LVD in the elderly. The conclusion was that BNP was a useful marker to exclude the presence of a disease, but that it had limited value in disease detection.

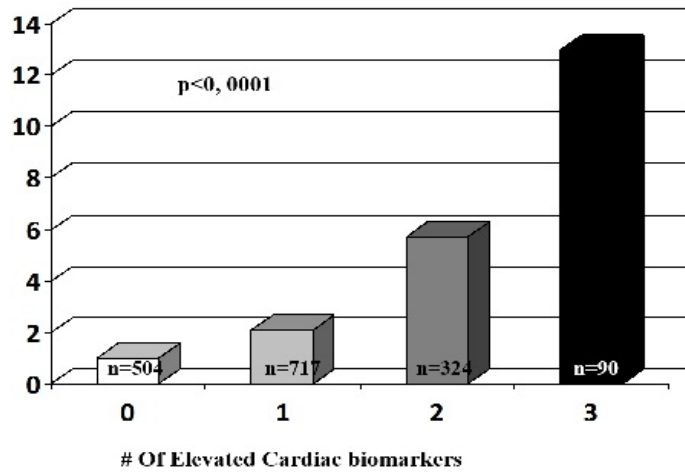
There is a high correlation (r=0.88) between the NT pro-BNP and BNP values, so that NT pro-BNP has a diagnostic value similar to BNP. NT pro-BNP may be a more sensitive marker than BNP to discover early LVD, over time they will provide more detailed results (3). A high level of neurohormonal factors (natriuretic peptides, norepinefrin, renin, endothelin 1), also emphasized by Tsutomoto et al (7), are showing that BNP is the only



**Graph 1.** The Incidence of Death, New or Progressive Congestive Heart Failure (CHF), and New or Recurrent Myocardial Infarction (MI) at 30 Days and 10 Months among Patients with B-Type Natriuretic Peptide Levels above or at or below the Prespecified Threshold of 80 pg per Milliliter.(13)

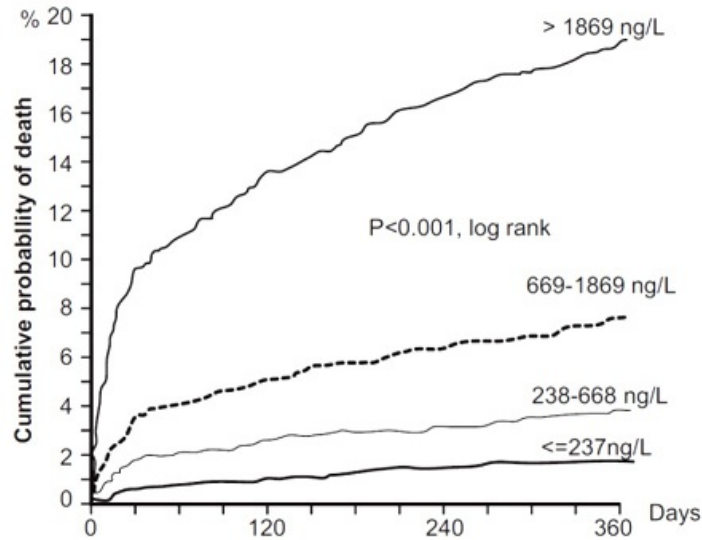


**Graph 2.1**

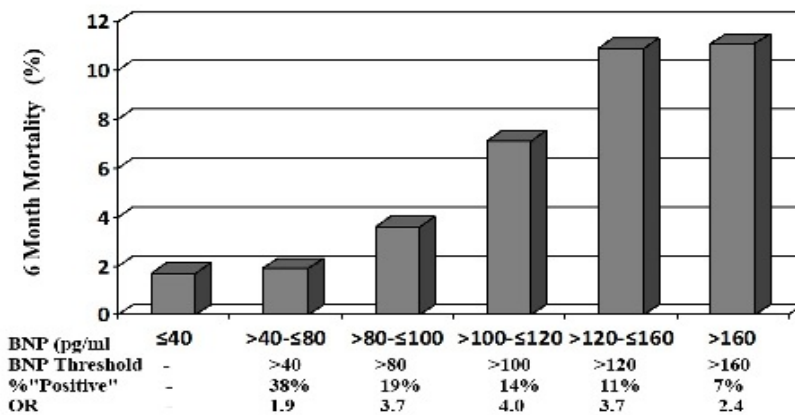


Graph 2.2

Graph 2.1, 2.2 Relative 30-Day Mortality Risk in OPUS-TIMI 16 (A) and TACTICS-TIMI 18 (B) in Patients Stratified by Number of Elevated Heart Markers (14)



Graph 3. Risk of death in patients with NSTEMI syndrome stratified by quartile of concentration Of NT-proBNP (Elecys 2010, Roche Diagnostics) at baseline (15)



Graph 4. Mortality Risk by BNP Stratified in Comparison with 40-160 pg/ml. (15)

neurohormonal marker for predisting heart failure progression (9). Patients with low plasma BNP concentrations have excellent long term prognosis. High concentrations of BNP are correlated with high mortality rates, almost 60% in a three-year observation period. Ioshihico et al., as well as recent reports have clarified the prognostic value of NT pro-BNP levels in patients with suspected ACS in emergency situations (10). NT pro-BNP level upon admission is not correlated with CKMB levels, troponin T and other heart markers for myocardial arrest. A unique diagnostic value was discovered (high specificity) of NT pro-BNP, especially in patients without an ST elevation of ACS reported in early acute phase (within 2 hours after the pain onset). The TIMI 18 study showed that biomarkers have a central role in the diagnosis and risk assessment in patients with NSTEMI. Three markers are classified for clinical assessment – troponin (as an ischemic confirmation marker), C-reactive protein (as an inflammatory marker) and BNP and NT pro-BNP (as chemodynamic function markers). According to numerous studies, BNP and NT pro-BNP are the best predictors of events within a thirty-day period after the acute event and within the following months. (4)

The prognostic value of NT pro-BNP in ACS patients was studied as part of a large cohort study by Omland et al. The NT pro-BNP level was highly correlated with long term mortality in patients with all cases of ACS. These studies showed that natriuretic peptides can be of importance in identifying patients with a more severe arrest and an eventual dysfunction of the left chamber.

Sabatine et al. used a multi-marker strategy in studying the predictability of adverse events in patients with ACS (BNP, hsCRP, TN T) within the OPUS-TIMI 16 and TACTIS-TIMI 18 study (Graph 2) (11). An increase in heart markers leads to an increase in a deadly outcome. A multi-marker analysis proved an independent prognostic importance for a triple end-point, seven-day mortality, myocardial arrest and six-month mortality.

Some newer analyses from the GUSTO IV study showed that compared to traditional risk factors and an ST depression, the NT pro-BNP level is a more significant parameter in the mortality prognosis (30 days and a year after ACS). Egers et al. observed the ACS risk 6 weeks, 6 months and 5 years after an acute coronary event and found that only NT pro-BNP after 6 months has a prognostic importance in the follow-up of patients with ACS. (Graph 3, Graph 4). In the FRISC II study, it was shown that NT pro-BNP determination 24 hours after an acute coronary event has a prognostic importance in further disease course after 6 months, with a high reliability rate in the development and prognosis. The level of peptides decreases with improved treatment and function of the left chamber (LC) and heart function (12).

### Implications

The goal of the study was to show that heart function markers have a role in the ACS setting. Furthermore, the study assessed the severity of clinical picture, complications, and possible relapses of the coronary event.

### Conclusion

Regardless of the time of sampling, the level of NT pro-BNP is correlated with mortality.

Risk assessment now includes the evaluation of the risk of new cardiac events, which cannot be predicted based on clinical condition in admission to the emergency department.

Determination of natriuretic peptide is a useful supplement to the standard clinical trial.

Patients with elevated troponin, CKMB, NT pro-BNP, BNP and NSTEMI have worse prognosis than those with unstable angina pectoris.

There is a direct connection between the level of troponin in serum, levels of BNP and NT pro-BNP with the risk of new coronary event or death.

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## ZNAČAJ ODREĐIVANJA BNP I NT pro-BNP KOD BOLESNIKA SA AKUTNIM KORONARNIM SINDROMOM

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Pod pojmom akutnog koronarnog sindroma podrazumeva se grupa različitih kliničkih stanja koja nastaju kao posledica akutne ishemijske ili nekroze miokarda, čiji je uzrok najčešće akutna koronarna lezija nastala rupturom aterosklerotskog plaka u koronarnoj arteriji sa pratećom trombozom, inflamacijom, vazokonstrikcijom i mikroembolizacijom.

Akutni koronarni sindrom se može ispoljiti kao nestabilna angina pectoris, akutni infarkt miokarda, sa i bez ST elevacije ili kao iznenadna srčana smrt.

Određivanje markera srčanog oštećenja u serumu ima naročitog značaja u potvrđivanju dijagnoze akutnog infarkta miokarda bez ST elevacije. Svako povišenje kardiospecifičnih enzima označava miokardnu nekrozu i ispunjava uslove za postavljanje dijagnoze akutnog infarkta miokarda. Larsen i saradnici su testirali značaj BNP, a Btzino i saradnici NT pro-BNP kod bolesnika sa akutnim koronarnim sindromom. Visok nivo natriuretskih peptida ukazuje na veliki rizik od nastanka kardioloških komplikacija.

Ovaj prikaz treba da pokaže značaj i efikasnost određivanja biohemijskih markera kod bolesnika sa AKS, značaj u postavljanju dijagnoze, proceni terapijskog pristupa u zavisnosti od težine kliničke slike kao i stratifikacije rizika od ponovnog koronarnog događaja.

Ovaj rad ukazuje na značaj određivanja BNP i NT pro-BNP kao novih dijagnostičkih i terapijskih metoda u zbrinjavanju bolesnika sa AKS.

Markeri srčane funkcije imaju ulogu u postavljanju dijagnoze AKS, kao i proceni težine kliničke slike bolesti, komplikacija i mogućih ponovnih koronarnih događaja. *Acta Medica Medianae 2016;55(4):21-27.*

**Ključne reči:** akutni koronarni sindrom, biohemijski markeri, natriuretski peptidi, BNP, NT pro-BNP