# Admission B-type natriuretic peptide level predicts long-term survival in low risk ST-elevation myocardial infarction patients

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# Abstract

**Background:** In patients with acute myocardial infarction (AMI), B-type natriuretic peptide (BNP) is a predictor of short- and medium-term mortality.

**Aim:** To evaluate the long-term prognostic value of a single measurement of plasma BNP in low risk patients with first ST-elevation myocardial infarction (STEMI).

**Methods:** Plasma BNP concentrations were analysed on admission in 211 patients, median age 68 (56.0–75.0) years, admitted with first STEMI and treated with primary percutaneous coronary intervention (PPCI). Left ventricular ejection fraction (LVEF) was assessed by echocardiography during the first 24 h. Patients were followed for a median 48.2 (42.3–72.6) months.

**Results:** The median BNP level was 92.5 (36.3–199.2) pg/mL. During the follow-up period, 79.6% of patients survived. Logistic regression analysis indicated that among the assessed clinical, biochemical, angiographic and echocardiographic parameters, the best predictors of mortality were age, LVEF, maximal creatinine concentration and BNP measurements, (p < 0.05). In multivariate Cox regression analysis for the prediction of death, only age remained significant (p = 0.00007). Admission BNP level > 400 pg/mL indicated patients with the highest risk of death (47.1% vs 22% and 18.4% in patients with BNP level < 100 pg/mL and 100–400 pg/mL, respectively; p < 0.05).

**Conclusions:** A single measurement of BNP on admission can improve long-term risk stratification in low risk first STEMI patients treated with PPCI.

Key words: B-type natriuretic peptide, STEMI, mortality

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### **INTRODUCTION**

Natriuretic peptides, especially B-type natriuretic peptide (BNP), are a valuable addition to standard clinical assessment in the diagnosis and prognosis of heart failure (HF) [1]. In acute coronary syndromes (ACS), elevated baseline levels of BNP predict cardiovascular (CV) events during short- and long-term follow-up [2, 3]. The BNP has also been shown to be an in-

dependent predictor for death in heterogenous populations of patients with acute myocardial infarction (AMI) [4–6]. However, the prognostic potential of BNP with respect to longterm all-cause mortality in low risk patients with ST-elevation MI (STEMI) treated invasively, and without history of previous CV diseases or symptoms of HF, seems not to have been investigated.

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Therefore, the aim of this study was to assess the incremental prognostic value of BNP in a selected group of first STEMI patients treated invasively with primary percutaneous coronary intervention (PPCI).

#### **METHODS**

#### Patient population and follow-up

The study patients were selected out of 530 first STEMI patients. The detailed characteristics of the population studied have been described elsewhere [7]. Briefly, 211 patients (median age 68 years; 25th-75th percentile: 56.0-75.0; 70.3% men), with symptoms of first STEMI treated with PPCI were included in the study. Exclusion criteria were: history of previous MI, severe valvular disease, cardiomyopathy, any form of congenital cardiac disease or symptoms of chronic HF. The characteristics of the whole study patients are shown in Table 1. The diagnosis of STEMI was made on the basis of recent European Society of Cardiology (ESC) recommendations [8]. On admission, the following clinical parameters were assessed: heart rate, systolic and diastolic blood pressures, and Killip classification. For each patient, a time interval from chest pain onset to admission was recorded, and the Thrombolysis in Myocardial Infarction (TIMI) Risk Score for STEMI [9] was calculated. Moreover, the following parameters (mostly related to the infarct size) were assessed: localisation of MI, the type of the infarct-related artery (IRA), and the maximal activity of serum creatine kinase myocardial isoenzyme (CK-MB). Maximal concentrations of serum creatinine and C-reactive protein (CRP), as strong predictors of mortality in MI [10, 11], were also measured. Within the first 24 h, each of the patients underwent standard trans-

Table 1	. Characteristics	of the whole	study patients
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Age [years]*	68.0 (56.0–75.0)		
Death	43 (20.4%)		
HR [bpm]*	75.0 (68.0–90.0)		
SBP [mm Hg]*	140.0 (120.0–160.0)		
DBP [mm Hg]*	90.0 (80.0–100.0)		
Killip class*	1 (1–2)		
TIMI Risk Score for STEMI*	3 (2–5)		
Time from chest pain onset	4 (2–6)		
to admission [h]*			
BNP [pg/mL]*	92.5 (36.3–199.2)		
Maximal CK-MB [IU/L]*	181.5 (87.0–291.7)		
Maximal creatinine [mg/dL]*	1.0 (0.8–1.2)		
CRP [mg/L]*	16.6 (8.1–34.0)		
LVEF [%]*	48.0 (40.0–53.0)		

\*Median (25<sup>th</sup>–75<sup>th</sup> percentile); BNP — B-type natriuretic peptide; HR heart rate; SBP — systolic blood pressure; DBP — diastolic blood pressure; CK-MB — creatine kinase myocardial isoenzyme; CRP — C-reactive protein; LVEF — left ventricular ejection fraction thoracic echocardiography (TTE) with the assessment of left ventricular ejection fraction (LVEF). Blood samples for BNP assessment were obtained on admission. According to the current guidelines, for the diagnosis of HF symptoms according to BNP concentrations, we divided the whole study group into three subgroups — group 1: < 100 pg/mL, group 2: 100–400 pg/mL and group 3: > 400 pg/mL [12].

Details of PPCI as well as pharmacotherapy during hospitalisation have been described elsewhere [7]. All patients had a PPCI procedure within 12 h of the onset of chest pain.

Patients were followed for a median of 48.2 months (range 42.3–72.6). The analysed end-point was total mortality. Data concerning mortality were obtained from the local population registry run by a Government Office.

This investigation conforms with the principles outlined in the Declaration of Helsinki and was approved by the local institutional committee on human research (Institutional Review Board — Local Bioethics Committee of Bialystok Medical University). Informed consent was obtained from all patients.

### Blood sampling and measurements of BNP

Venous blood samples were collected using a S-Monovette blood collection system with EDTA as anticoagulant for determination of BNP. Blood samples for BNP were centrifuged at 3,500 g to obtain plasma samples. Plasma samples were separated, aliquoted and stored at -80°C until assayed.

Plasma levels of BNP were measured using microparticle enzyme immunoassay kits (MEIA, Abbott, Chicago, IL, USA, Architect Ci8200). The intra-assay CV percentage for BNP is claimed by the manufacturer of assay kits to be 5.9% at BNP mean concentration of 29.2 pmol/L, SD = 6.0.

#### Statistical analysis

The results are expressed as medians with 25% to 75% interquartile ranges (continuous variables) or as proportions (categorical variables). Associations between continuous and categorical variables were examined using the Kruskal-Wallis ANOVA range test and associations between categorical variables using  $\chi^2$  test. The Kaplan-Meier analysis was performed to assess differences in mortality according to BNP levels. Proportional hazard Cox regression was used to determine associations between mortality and independent variables. This method was used to identify the best predictor. All analyses were carried out using Statistica 9.1 (StatSoft, Tulsa, OK, USA) software. A p value < 0.05 was considered statistically significant.

# RESULTS

The baseline characteristics of the whole study patients are set out in Table 1. During follow-up, 43 (20.4%) patients died (168 patients survived). Patients with the highest BNP measurements were significantly older, compared to lower BNP levels groups (Table 2). Moreover, patients with the highest

Characteristics	BNP < 100 pg/mL	BNP 100–400 pg/mL	BNP > 400 pg/mL	Р
	(n = 114)	(n = 72)	(n = 25)	
Age [years]*	62.0 (53.0–71.0)	72.0 (63.0–78.0)	77.0 (69.5–80.0)	0.00001
Men	85 (75%)	44 (61%)	18 (72%)	0.10
Death	22 (19%)	12 (17%)	9 (36%)	0.11
HR [bpm]*	75.0 (65.0–90.0)	76.0 (69.0–90.0)	76.0 (70.0–98.0)	0.80
SBP [mm Hg]*	140.0 (120.0–165.0)	140.0 (120.0–160.0)	135.0 (120.0–155.0)	0.50
DBP [mm Hg]*	90.0 (80.0–100.0)	85.0 (80.0–100.0)	80.0 (70.0–90.0)	0.41
Killip class*	1 (1–2)	1 (1–2)	1 (1–2)	0.06
TIMI Risk Score for STEMI*	3 (1–5)	4 (3–6)	5 (4–6)	0.00001
Time from chest pain onset to admission [h]*	3 (2–5)	4 (3–6.5)	6 (4–12)	0.001
Localisation of MI:				0.35
Anterior	34 (30%)	26 (36%)	10 (40%)	
Inferior	59 (52%)	33 (46%)	10 (40%)	
Lateral	4 (3%)	2 (3%)	0 (0%)	
Other	17 (15%)	11 (15%)	5 (20%)	
IRA:				0.11
LAD	37 (32.4%)	34 (47.2%)	11 (44%)	
LCx	53 (46.5%)	27 (37.5%)	7 (28%)	
RCA	10 (8.8%)	8 (11.1%)	3 (12%)	
Other IRA*	14 (12.3%)	3 (4.2%)	4 (16%)	
Maximal CK-MB [IU/L]*	192.0 (101.0–289.0)	177.0 (91.0–320.0)	122.0 (47.5–297.0)	0.55
Maximal creatinine [mg/dL]*	0.9 (0.8–1.2)	1.0 (0.8–1.1)	1.0 (0.9–1.2)	0.49
CRP [mg/L]*	15.5 (9.0–26.8)	17.1 (8.1–36.4)	26.9 (5.0–114.9)	0.27
LVEF [%]*	50.0 (45.0–55.0)	47.5 (40.0–50.0)	40.0 (32.0–45.5)	0.00001

Table 2. Characteristics of three subgroups divided according to BNP levels

\*Median (25<sup>th</sup>-75<sup>th</sup> percentile); STEMI — ST-elevation myocardial infarction; IRA — infarct-related artery; LAD — left anterior descending; LCx — left circumflex; RCA — right coronary artery; Other IRA\* — posterior descending artery, intermediate artery, obtuse marginal, diagonal branch; rest of abbreviations as in Table 1

BNP levels had longer time of chest pain, higher TIMI Risk Score and the lowest LVEF. There was no difference between admission Killip class among the groups. Overall, the patients with the highest BNP level also had the highest mortality (more than one third of them died), although this was not significant (Table 2).

### Cox logistic regression analysis

Among clinical, biochemical (maximal CK-MB activity, CRP, maximal creatinine and admission BNP concentrations), as well as angiographic and echocardiographic parameters, the analysis of logistic regression performed for the whole study group indicated that the highest risk of death was found for age (odds ratio [OR] = 1.1; 95% confidence interval [CI] 1.0–1.1, p = 0.00001); maximal creatinine concentration (OR = 1.2; 95% Cl 1.0–1.3, p = 0.04); LVEF (OR = 0.8; 95% Cl 0.7–0.9, p = 0.009) and BNP measurements (OR = 2.5; 95% Cl 1.2–5.1, p = 0.02) (Fig. 1). Of those significant parameters in multivariate Cox regression analysis for the prediction of death, only age remained significant (p = 0.00007).

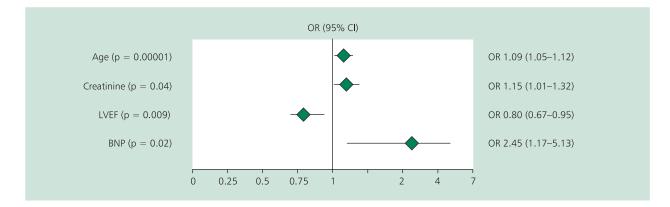
#### Kaplan-Meier analysis

The risk of death during follow-up increased with increasing levels of BNP measured on admission, as in Figure 2. In group 1 (BNP < 100 pg/mL) and group 2 (BNP 100–400 pg/ /mL), the survival was 78% and 81.6%, respectively (1 vs 2: p = 0.07), while in group 3 (BNP > 400 pg/mL) survival has fallen to 52.9% (1 vs 3: p = 0.03 and 2 vs 3: p = 0.04; Fig. 2).

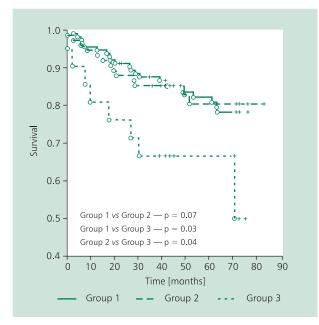
#### **DISCUSSION**

Our aim was to study the long-term predictive value of BNP in a selected group of STEMI patients. Our major finding is that a single measurement of BNP on admission is a strong predictor of long-term all-cause mortality in a low-risk group of patients with first STEMI treated invasively. Our results suggest that patients with the highest admission BNP concentrations carry the highest risk of death: more than one-third of them died within the next 3–6 years after MI.

Natriuretic peptides as prognostic tools in HF patients have an unquestionable role. Furthermore, previous studies have demonstrated that BNP is a predictor of short- and long-



**Figure 1.** Cox logistic regression: the associations between mortality and independent variables; LVEF — left ventricular ejection fraction; BNP — B-type natriuretic peptide; OR — odds ratio; CI — confidence interval



**Figure 2.** Kaplan-Meier survival curves: the differences in survival according to B-type natriuretic peptide (BNP) levels: group 1: BNP < 100 pg/mL (n = 112); group 2: BNP 100– -400 pg/mL (n = 72); group 3: BNP > 400 pg/mL (n = 25)

-term mortality in patients with ACS and after MI [13, 14]. The BNP measured after AMI was a powerful predictor of CV mortality [6].

In contrast to previous studies, we decided to select a group of first STEMI patients without CV co-morbidities and without previous symptoms of HF, who were successfully treated with PPCI within 12 h of the onset of chest pain. Szadkowska et al. [15] evaluated a similar group of low-risk first STEMI patients with one-vessel disease, successfully treated with PPCI. However, in this group of patients NT-proBNP was measured within the first 4–5 days and occured to be the strongest predictor of early LV dysfunction.

In the present study we attempted to assess the long--term prognostic value of BNP measured very early — in an acute phase of STEMI, before IRA was opened. In the acute phase of MI, BNP rises rapidly and peaks within 24-36 h. It depends, however, on the type of MI (NSTEMI or STEMI) as well as on the success of the reperfusion therapy [16]. On the other hand, Grabowski et al. [5] have shown that admission BNP seems to be not only an independent predictor of short--term mortality in STEMI patients, but also of angiographic success after PCI. The selection of our patients could help to evaluate the relationship between mortality and BNP values purely related to an index of STEMI. In our patients, BNP was assessed before PPCI, thus it could estimate long-term mortality independently of the success of reperfusion therapy as well as of myocardial perfusion (myocardial 'blush' as assessed after PCI). Thus, the fact that BNP was obtained before reperfusion therapy could explain why it was not significant in multivariate analysis.

Overall, this was a low risk group of STEMI patients (as assessed by TIMI Risk Score). The long-term mortality rate was around 20%. Patients with the highest BNP concentrations had the lowest LVEF, which was predictive in univariate analysis. Natriuretic peptides have been suggested to correlate with impaired LV function [17] and have been shown to be predictors of LV dysfunction and two-year survival in the course of MI [18]. However, in our study, BNP measurements were performed shortly after admission and TTE with LVEF assessment was accomplished within the first 24 h. Moreover, most of our patients had preserved LVEF. This may explain why LVEF was a predictor of mortality in univariate analysis, but was not an independent predictor of outcome in multivariate analysis. On the other hand, patients with ischaemic heart disease also exhibit increased plasma BNP concentrations despite preserved cardiac function, and elevated natriuretic peptides are independent predictors of clinical events in patients with HF and preserved LV function during a follow-up time of almost 1.5 years [19, 20]. Interestingly, patients with the highest BNP concentrations (> 400 pg/mL) had the lowest LVEF, but also the lowest CK-MB activity. This may be explained not only by longer delay from chest pain onset to admission, but also by angiographic success (assessed by TIMI flow grade). This requires further evaluation.

Björklund et al. [21] found that one-year mortality increased stepwise according to increasing concentrations of NT--proBNP in STEMI patients treated with fibrinolytic therapy. Moreover, they showed that Killip class provided no independent prognostic information according to all-cause mortality when NT-proBNP was added to the multivariate model. These results are similar to ours; however, our patients were treated invasively and had a much longer follow-up period. Of all the major clinical predictors such as age, admission symptoms of HF, parameters related to the infarct size, including biochemical measurements (maximal CK-MB activity, maximal creatinine and CRP concentrations) and echocardiographic assessments, the differences among three BNP groups were present only according to age, the time from the start of symptoms to admission, TIMI Risk Score and LVEF. Plasma BNP, serum creatinine concentration, LVEF and age were predictive only in univariate analysis. It is worth noting that even BNP was not an independent predictor of mortality. Based on the previous reports, these parameters are known to be strong and independent predictors of mortality in patients with HF and coronary artery disease, including acute phase of MI [3, 22, 23]. In our study, only age finally became an independent risk factor: in multivariate analysis neither BNP, creatinine concentration, nor LVEF were predictive. On the other hand, because only patients with the highest BNP concentrations (> 400 pg/mL) had the longest delay from the onset of chest pain to admission, the highest TIMI Risk Score as well as the lowest LVEF, this may identify the group of patients with more advanced symptoms of chronic HF, which influenced the rate of their survival. The worst prognosis in patients with the highest BNP concentration could be related to the signs of HF that occurred very early in an acute phase of MI, before the appearance of the clinical symptoms.

Of all the analysed parameters, only advanced age remained an independent predictor of long-term mortality. In the context of previous studies, this result is unusual. Jernberg et al. [24] performed early risk stratification among heterogeneous, unselected patients with ACS and no ST-segment elevation. In a multivariate analysis, increasing age, together with creatinine concentration, diabetes, ECG changes and elevated troponin levels, were independent predictors of outcome in the follow-up of 3.3 years. An elevated level of natriuretic peptide was an independent predictor of mortality when adjusted to clinical background factors, ECG changes and troponin levels. Likewise in STEMI patients, age, together with other assessed clinical parameters, was associated with 30-day mortality, but only in univariate analysis [25].

However, after the adjustment of major predictors of mortality and when the population was restricted to those with no history of chronic HF, the independent relationship with BNP was unaltered. On the other hand, in an unselected group of more than 500 consecutive STEMI patients treated with PPCI, TIMI for STEMI and other risk scores were predictive for five-year mortality, which was around 16% [26]. The selective, not high risk, group of studied patients and, compared to previously published studies, a longer follow--up, could explain our results. However, as in a previous trial, BNP was predictive in patients without previous MI and signs of HF on admission [27].

#### Limitations of the study

There are some limitations of the present study. We did not support the value of combining BNP with established clinical, biochemical and echocardiographic parameters for risk assessment. This might be due to a selective type of patients studied and the very long follow-up. Moreover, early BNP evaluation in the course of STEMI could influence these results. In our previous report, only BNP measured on the fifth day after STEMI was predictive for complications within a oneyear observation [7]. In addition, in patients with anterior STEMI undergoing PPCI, only discharge NT-proBNP (together with a combined assessment of myocardial contrast perfusion, T-wave alternans and CK-MB) predicted the risk of complications in a two year follow-up [28]. Thus, it might be valuable to assess BNP later as well as to perform later estimation of LV function, and to compare those two strong predictors of survival with the values performed shortly after admission. Nevertheless, the patients were carefully selected and thoroughly investigated, and so we believe that the obtained results are representative.

#### **CONCLUSIONS**

Our study shows that in low-risk first STEMI patients, treated with PPCI, elevated levels of BNP at presentation are associated with impaired long-term survival. We suggest that this might be related to early HF, which occurred before overt clinical signs and symptoms. In this group of patients, BNP measurement on admission can identify a low- or high-risk group of death in long-term observation.

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Conflict of interest: none declared

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# Pojedynczy pomiar peptydu natriuretycznego typu B pozwala na określenie rokowania w zawale serca z uniesieniem odcinka ST u pacjentów niskiego ryzyka

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## Streszczenie

**Wstęp:** Peptyd natriuretyczny typu B (BNP) jest ważnym wskaźnikiem śmiertelności w obserwacji krótko- i średnioterminowej u pacjentów z ostrym zawałem serca.

**Cel:** Celem pracy była ocena znaczenia rokowniczego pojedynczego pomiaru BNP w ocenie ryzyka śmiertelności odległej w grupie niskiego ryzyka u chorych z zawałem serca z uniesieniem odcinka ST (STEMI).

**Metody:** Osoczowe stężenia BNP (MEIA) mierzono przy przyjęciu u 211 pacjentów z pierwszym STEMI (mediana wieku 68 lat, 56–75 lat), leczonych interwencyjnie metodą pierwotnej angioplastyki wieńcowej (PPCI). Frakcję wyrzutową lewej komory (LVEF) oceniano echokardiograficznie w pierwszej dobie pobytu w szpitalu. Okres obserwacji odległej wyniósł średnio 48,2 miesiąca (42,3–72,6 miesiąca).

**Wyniki:** Wyjściowa mediana stężenia BNP wynosiła 92,5 (36,3–199,2) pg/ml. W czasie obserwacji długoterminowej przeżyło 79,6% pacjentów. Analiza regresji logistycznej wykazała, że spośród klinicznych, biochemicznych, angiograficznych i echokardiograficznych czynników wpływających na rokowanie najwyższa śmiertelność wiązała się z wiekiem, LVEF, maksymalnym stężeniem kreatyniny i BNP (p < 0,05). Jednak w modelu regresji wieloczynnikowej Coxa jedynie wiek pozostawał istotny statystycznie (p = 0,00007). Analiza przeżycia metodą Kaplana-Meiera wykazała, że wartości BNP > 400 pg/ml wiążą się z najwyższą śmiertelnością odległą (47,1% v. 22% i 18,4% w grupie chorych z BNP < 100 pg/ml i 100–400 pg/ml; p < 0,05).

Wnioski: Pojedynczy pomiar stężenia BNP przy przyjęciu u chorych niskiego ryzyka z pierwszym STEMI leczonych PPCI stanowi ważny czynnik prognostyczny w obserwacji odległej.

Słowa kluczowe: peptyd natriuretyczny typu B, zawał serca z uniesieniem odcinka ST, śmiertelność

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