

# Brain natriuretic peptide levels predict morbidity and mortality in haemodialysis patients

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## ABSTRACT

**Background:** Brain natriuretic peptide is a predictor of mortality in multiple cardiovascular diseases but its value in patients with chronic kidney disease is still a matter of debate.

**Patients and methods:** We studied 48 haemodialysis patients with mean age  $70.0 \pm 13.9$  years, 62.5% female, 43.8% diabetics, with a mean haemodialysis time of  $38.1 \pm 29.3$  months.

To evaluate the role of brain natriuretic peptide as a prognostic factor in this population we performed a two-session evaluation of pre- and post-mid-week haemodialysis plasma brain natriuretic peptide concentrations and correlated them with hospitalisation and overall and cardiovascular mortality over a two-year period.

**Results:** There were no significant variations in pre- and post-haemodialysis plasma brain natriuretic peptide concentrations. Pre- and post-haemodialysis brain natriuretic peptide concentrations were significantly greater in patients who died from all causes ( $p=0.034$  and  $p=0.001$ , respectively) and from cardiovascular causes ( $p=0.043$  and  $p=0.001$ , respectively). Patients who were hospitalised in the two-year study period also presented greater pre- and post-haemodialysis brain natriuretic peptide concentrations ( $p=0.03$  and  $p=0.036$ , respectively). Patients with

mean brain natriuretic peptide concentrations  $\geq 390$  pg/mL showed a significantly lower survival at the end of the two-year study period.

**Conclusion:** Brain natriuretic peptide was a good predictor of morbidity and mortality (overall and cardiovascular) in our population.

### Key-Words:

Brain natriuretic peptide; haemodialysis; mortality.

## INTRODUCTION

Brain natriuretic peptide (BNP) belongs to a natriuretic peptide family composed of four peptide hormones: atrial natriuretic peptide (ANP), BNP, C-type natriuretic peptide and urodilatin<sup>1,2</sup>. The tissue-specific distribution and regulation of each of these hormones is different, but their cardinal effect is natriuresis and diuresis, induced by increased glomerular filtration and increased excretion of Na<sup>+</sup> ions in renal tubules<sup>1-3</sup>.

BNP is secreted mainly in cardiomyocytes from the left ventricle and is also partly produced in certain areas of the brain. BNP is synthesised as a prohormone which is cleaved during transfer across the membrane of cardiomyocytes into the biologically active BNP (one peptide chain of 32

amino acids, molecular weight of 3.4 kDa) and the biologically inactive amino-terminal fragment of proBNP – N-terminal proBNP (NT-proBNP) (peptide chain of 76 amino acids, molecular weight of 8.5 kDa). Plasma concentrations of these two markers are affected by their different half-lives. BNP has a half-life of about 23 minutes; NT-proBNP has a significantly longer half-life (between 60 and 120 minutes)<sup>3</sup>. The level of NT-proBNP is therefore higher. Both peptides can be measured immunochemically.

Extension of cardiomyocytes represents a signal for BNP release into the circulation. BNP is bound to a signal receptor (NPR-A) that induces the increase of cGMP in the cell. This is accompanied by a potent diuretic, natriuretic and vascular smooth muscle-relaxing effect as well as by a complex of interactions with the neurohormonal system (e.g. inhibition of renin and aldosterone synthesis)<sup>3,4</sup>. In addition to glomerular filtration, BNP is eliminated from plasma mainly through natriuretic peptide receptors (NPR-C) and degraded by neutral endopeptidases. In contrast, NT-proBNP is largely eliminated by glomerular filtration only<sup>5</sup>. This explains the strong influence of renal function mainly on NT-proBNP concentrations. This is also true for BNP, but to a much lesser extent.

The clinical benefit to using these circulating biomarkers to screen for cardiovascular (CV) risk has been well documented in the general population<sup>6-8</sup>. BNP has been seen to act as a diagnostic marker for left ventricular hypertrophy, left and right ventricular dysfunction and heart failure<sup>6,7</sup>. In addition, BNP acts as a predictor of mortality in heart failure, post-myocardial infarction, unstable angina, *cor pulmonale* and primary pulmonary hypertension<sup>8</sup>. Patients with chronic kidney disease (CKD), including those on dialysis, have one of the highest CV risk scores. In this population, the clinical benefit of BNP and NT-proBNP measurements has not been well established<sup>9,10</sup>. The fact that patients with CKD stage 5 have significantly increased BNP and NT-proBNP levels<sup>5,9,10</sup> has been considered a major limitation to its use as a diagnostic tool.

The aim of this study was to evaluate the role of BNP as a prognostic factor in terms of morbidity and mortality in chronic haemodialysis (HD) patients.

## ■ PATIENTS AND METHODS

### ■ Study design

This was an observational and prospective study analysing prevalent chronic HD patients treated in a single centre over a two-year period.

### ■ Population

The study included 48 prevalent chronic HD patients. All patients were dialysed with high flux membranes (helixone-Fresenius®) and ultrapure water.

At baseline, mean age was 70.0±13.9 years and 37.5% of the patients were male. Mean HD time was 38.1±29.3 months.

### ■ Methods

A prior and current history of diabetes mellitus and/or hypertension was investigated in all patients. Coronary artery disease was diagnosed if the patient had a typical history of angina pectoris or had suffered a myocardial infarction, had a positive stress test or had undergone a percutaneous coronary intervention or coronary bypass surgery.

In the two-year period of the study, hospitalisation days as well as total and cardiovascular mortality were evaluated prospectively.

The levels of BNP were measured at the beginning of the study at two consecutive mid-week HD sessions. EDTA plasma samples collected pre- and post-HD were centrifuged and then stored at -20°C. The levels of BNP were measured using a peptide enzyme immunoassay (EIA) (Peninsula Laboratories, St. Helens, UK). Intra- and inter-assay variability were <5% and <14%, respectively.

BNP post HD plasma levels were corrected for possible haemoconcentration according to haematocrit changes during HD.

### ■ Statistical analysis

We used the  $\chi^2$ , Student or Mann Whitney tests for univariate analysis and logistic regression on

multivariate analysis (confidence interval of 95%) for the statistical analysis. Survival evaluation was performed with Cox regression models. Survival curves were performed using Kaplan–Meier with evaluation of log-rank. BNP cut-off value used in survival curves was determined via a receiver operating characteristic (ROC) curve. BNP used in survival analysis was mean BNP (mean of pre- and post-HD BNP values).

Statistical analysis was performed using SPSS system 14.0 (SPSS Inc., Chicago, IL) and the Medcalc program version 6.0 (Medcalc software, Mariakerke, Belgium). A  $p < 0.05$  was considered statistically significant for all comparisons.

## RESULTS

Of the 48 chronic HD patients evaluated, 43.8% ( $n=21$ ) had diabetes mellitus, 39.6% ( $n=19$ ) hypertension and 37.5% ( $n=18$ ) coronary artery disease.

Mean pre-HD BNP was  $377 \pm 158$  (105-697) pg/mL and mean post-HD BNP was  $382 \pm 169$  (111-784) pg/mL. Pre- and post-HD plasma BNP values were similar in the general group ( $p > 0.05$ ). Pre- and post-BNP plasma levels did not correlate with ultrafiltration volume during HD.

Pre- ( $422 \pm 168$  vs.  $350 \pm 147$ ;  $p=0.03$ ) and post-HD ( $456 \pm 164$  vs.  $337 \pm 158$ ;  $p=0.01$ ) BNP levels were higher in patients with coronary artery disease.

Values of pre- and post-HD BNP were similar in patients with diabetes and hypertension.

Thirty-one patients (64%) were hospitalised during the study period. Mean hospitalisation per patient was  $1.13 \pm 1.18$  days and mean hospitalisation days per patient were  $14.3 \pm 30.4$ . Mean levels of pre- ( $411 \pm 151$  vs.  $315 \pm 155$ ;  $p=0.03$ ) and post- ( $419 \pm 170$  vs.  $314 \pm 148$ ;  $p=0.036$ ) HD BNP were higher in patients that were hospitalised during the study. Sixteen (33%) died during the two years of the study, nine (56%) from CV causes. Patients who died from CV causes had higher levels of pre- ( $477 \pm 132$  vs.  $357 \pm 176$ ;  $p=0.043$ ) and post- ( $568 \pm 127$  vs.  $345 \pm 113$ ;  $p=0.001$ ) HD BNP. Also patients who died from overall causes had higher values of pre- ( $433 \pm 146$  vs.  $346 \pm 157$ ;  $p=0.034$ ) and post- ( $486 \pm 165$  vs.  $325 \pm 143$ ;  $p=0.001$ ) HD BNP (Fig. 1).

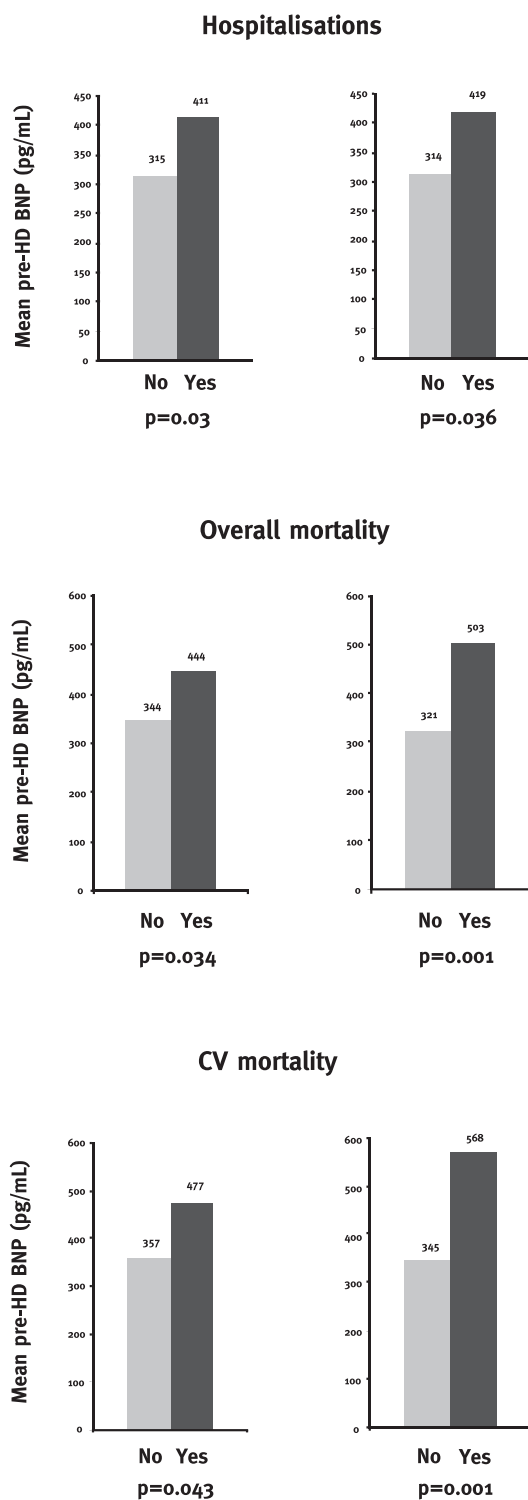
Multivariate analysis showed time on HD (OR: 1.8, 95% CI: 1.05 to 3.12,  $p=0.04$ ), coronary artery disease (OR: 3.3, 95% CI: 2.03 to 3.73,  $p=0.01$ ) and pre- (OR: 1.5, 95% CI: 1.10 to 1.57,  $p=0.04$ ) and post- (OR: 2.8, 95% CI: 1.25 to 7.34,  $p=0.03$ ) HD BNP were all positive predictors of hospitalisation. Time on HD (OR: 1.4, 95% CI: 1.08 to 1.53,  $p=0.04$ ), coronary artery disease (OR: 5.2, 95% CI: 1.70 to 13.52,  $p=0.009$ ) and pre- (OR: 2.1, 95% CI: 1.25 to 3.32,  $p=0.03$ ) and post- (OR: 4.3, 95% CI: 1.26 to 14.12,  $p=0.005$ ) HD BNP were also positive predictors of mortality from overall causes. Coronary artery disease (OR: 5.7, 95% CI: 1.94 to 14.37,  $p=0.005$ ) and pre- (OR: 1.8, 95% CI: 1.23 to 3.34,  $p=0.04$ ) and post- (OR: 2.9, 95% CI: 1.29 to 7.37,  $p=0.01$ ) HD BNP were positive predictors of mortality from CV causes (Table I).

**Table I**

Multivariate analysis (binary regression)

Dependent variable	Independent variables	OR	CI (95%)	p
Hospitalisations	time on HD	1.8	1.05-3.12	0.04
	coronary disease	3.3	2.03-3.73	0.01
	pre-HD BNP	1.5	1.10-1.57	0.04
	post-HD BNP	2.8	1.25-7.34	0.03
Overall mortality	time on HD	1.4	1.08-1.53	0.04
	coronary disease	5.2	1.70-13.52	0.009
	CRP	7.3	2.81-18.83	0.004
	pre-HD BNP	2.1	1.25-3.32	0.03
	post-HD BNP	4.3	1.26-14.12	0.005
CV mortality	coronary disease	5.7	1.94-14.37	0.005
	pre-HD BNP	1.8	1.23-3.34	0.04
	post-HD BNP	2.9	1.29-7.37	0.01

HD, haemodialysis; BNP, brain natriuretic peptide; CRP, C-reactive protein; CV, cardiovascular.



**Figure 1**  
Hospitalised patients who died from overall or cardiovascular causes had higher pre- and post-BNP level.

The cut-off level of BNP determined by ROC curve analysis was 390 pg/mL, with a sensitivity and a specificity of 68.8% and 87.1%, respectively. Kaplan-Meier analysis showed all cause and CV mortality (Fig. 2) was responsible for a significant lower survival in patients with mean BNP levels  $\geq 390$  pg/mL.

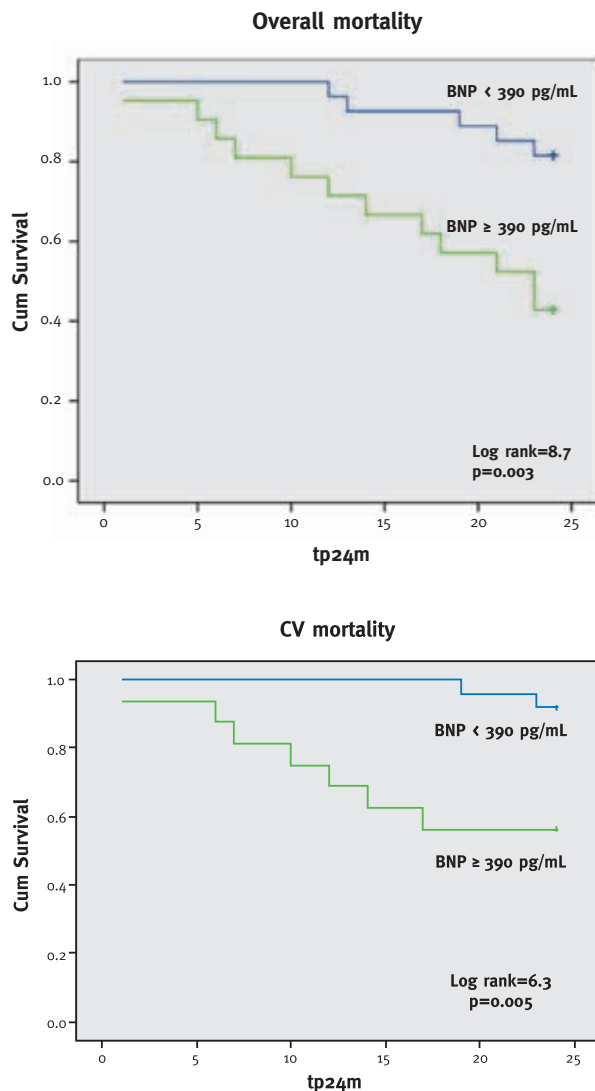
## DISCUSSION

This study demonstrated that increased plasma levels of BNP were good predictors of morbidity and mortality in chronic HD patients. Higher values of BNP were associated with more hospitalisations and higher mortality (overall and CV). Multivariate analysis showed pre- and post-BNP concentrations were independent positive predictors of hospitalisations and overall and CV mortality.

Taking a cut-off level of 300 pg/mL for CV risk used in the general population without renal disease<sup>8</sup> showed increased BNP levels in our population of chronic HD patients. This finding is in accordance with the results of several other researchers<sup>9,10</sup>. Our patients with BNP levels  $\geq 390$  pg/mL also had a significantly lower survival rate at the end of the two-year study period.

HD patients are generally in a latent state of cardiac dysfunction, even if they have no clinical signs, because these patients are exposed to ventricular overload and/or high blood pressure<sup>11,12</sup>. Alternatively, the increased plasma levels of BNP might only reflect the decreased clearance of the peptide from the circulation due to impaired glomerular filtration rate, rather than the increased synthesis and secretion of the peptides.

Many researchers have studied the behaviour of BNP levels during HD. According to Ishikura *et al.*<sup>13</sup>, plasma BNP levels did not significantly decrease after HD. Khose *et al.*<sup>14</sup> observed a slight decrease in BNP concentration during HD (9.3%). Nitta *et al.*<sup>15</sup>, Haugh *et al.*<sup>16</sup> and Clerico *et al.*<sup>17</sup> obtained similar results; intra-HD BNP decrease in their studies were 10, 13 and 16%, respectively. Other researchers mentioned a more pronounced fall in BNP levels during HD of 47%<sup>18</sup> and 67%<sup>19</sup>. Our results correspond to those of the first-mentioned study: pre- and post-HD BNP plasma levels were similar.



**Figure 2**

Lower survival in relation to overall and cardiovascular mortality in patients with BNP levels  $\geq 390$  pg/mL (Kaplan-Meier analysis)

BNP is removed with both low and high-flux HD, but this is probably accompanied by an intra-HD increase of this marker. One of the causes of increased BNP production during HD may be the negative correlation between BNP and left ventricular ejection fraction (LVEF). LVEF is a significant factor influencing the variation of this peptide during HD, so we can assume that HD triggers increased production of BNP in patients with impaired LVEF. Zeng *et al.*<sup>20</sup> also showed that, regardless of status

of left ventricular function, a significant increase in plasma BNP was observed ten minutes after HD with a decrease three hours after HD. These authors postulate that volume depletion may result in a relative increase in BNP concentration in the bloodstream. The BNP reduction three hours after HD is probably the result of relieved hypervolaemia, alleviating ventricular overload and diminishing either the myocardial synthesis or release of BNP.

Unlike ANP levels, some studies demonstrate that BNP concentrations do not correlate well with changes in volume status<sup>14,21</sup>. In our study, there was no correlation between BNP plasma levels and ultrafiltration volume.

Naganuma *et al.*<sup>22</sup> found that BNP plasma concentration was significantly higher in HD diabetic patients than in non-diabetic patients. Our results did not confirm that diabetic patients on HD have higher BNP levels. As expected, in this study plasma BNP levels were higher in patients with coronary disease.

CV events are a major cause of morbidity and mortality in HD patients. Chronic volume overload predisposes these patients to left ventricular hypertrophy, which, in turn, leads to congestive heart failure, malignant arrhythmias and sudden death<sup>23,24</sup>. Because natriuretic peptides are released in response to increased atrial and ventricular stretch and are affected by cardiac function<sup>2-4</sup>, elevated levels of these biomarkers can be used to predict future cardiac events and overall morbidity and mortality in HD patients.

The prognostic value of BNP levels in CKD patients has already been studied. Mallamaci *et al.*<sup>25</sup> found that BNP can help to identify dialysis patients with left ventricular hypertrophy. Catalotti *et al.*<sup>26</sup> described that plasma BNP concentration correlated better with left ventricular hypertrophy than with congestive heart failure in HD patients. A positive correlation with left ventricular mass and a negative correlation with LVEF has also been described<sup>27</sup>. Naganuma *et al.*<sup>22</sup> found that BNP levels also correlated with coronary disease in dialysis patients. Another study also showed that BNP plasma levels correlated positively with pulse pressure, left ventricular mass index and with the presence of more vascular calcifications<sup>28</sup>.

Some studies have shown that elevated levels of BNP indicate an increased risk of cardiac events in HD patients. According to Goto *et al.*<sup>29</sup>, increased BNP in HD patients is linked to increased risk of cardiac death. Similar results were obtained by Ishii *et al.*<sup>30</sup>, who also described that cardiac troponin T levels have a similar significance in these patients. Zoccali *et al.* consider natriuretic peptides useful for risk stratification of HD patients as they can predict overall and CV mortality<sup>27</sup>.

In recent studies<sup>31,32</sup>, NT-proBNP has also proven itself a useful marker of CV disease. Unlike BNP, NT-proBNP levels seem to be affected by ultrafiltration volume as well as HD membrane type, namely membrane pore size<sup>32,33</sup>. In spite of this, diagnostic accuracy of NT-proBNP can be similar to BNP if only pre-HD levels are used<sup>33</sup>.

Our results are in accordance with these prior studies and clearly suggest that basal BNP plasma levels are a useful non-invasive marker of long term morbidity and mortality in HD patients. Identifying dialysis patients at increased risk of cardiac events may improve their prognosis.

**Conflict of interest statement.** None declared.

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