

ORIGINAL ARTICLE

RETROSPECTIVE LOOK AT CHANGE IN BRAIN NATRIURETIC PEPTIDE VALUES IN AMBULATORY PATIENTS WITH CHRONIC HEART FAILURE

Wahla AS, Pascual R*, Rafeq Z[†], Joseph J^{††}

Department of Internal Medicine, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan,

*Division of Pulmonary and Critical Care Medicine, Wake Forest University Baptist Medical Centre, Wake Forest University Baptist Medical Centre, Winston Salem, NC, [†]Department of Medicine, University of Massachusetts Worcester Medical Centre, Worcester, MA.

^{††}Division of Cardiology, West Roxbury Veterans Affairs Hospital, Boston University, Boston Medical Centre, Boston, MA

Background: There is significant interest in the role of B-type natriuretic peptide (BNP) guided therapy for outpatient congestive heart failure (CHF) patients. The objective of this study was to see if the percentage change in BNP levels can predict CHF hospitalisations or death. **Methods:** We retrospectively reviewed the records of CHF patients who had BNP levels drawn on two clinic visits. Patients were divided into two groups, those with a 70% or greater increase in the BNP values and those in whom the BNP value either decreased or did not increase by 70%. Primary outcome measured was the need for hospitalisation for CHF or death within 6 months of the second clinic visit. **Results:** One hundred and fourteen (114) paired BNP measurements were included in the analysis. Of these, 26 had >70% increase in BNP while 88 did not. Hospitalisations for CHF or death at 6 months were significantly higher in the former group than the latter ($p=0.04$). On multivariate regression analysis significant change in BNP remained a predictor of adverse outcomes. **Conclusions:** In stable outpatients with CHF, >70% increase in BNP is an independent risk factor for CHF hospitalisations or death at 6 months.

Keywords: Congestive heart failure, B-type natriuretic peptide, outpatient, hospitalisation

INTRODUCTION

In recent years there has been increased interest in the use of routine B-type natriuretic peptide (BNP) testing to aid in the outpatient management of Chronic Heart failure (CHF) patients. The Valsartan Heart Failure Trial (Val-HeFT) which evaluated the efficacy of valsartan in patients with moderate to severe CHF also involved measurement of blood BNP levels.¹ They observed a direct relationship between percent change in BNP and adverse outcomes. Latini *et al*² using the same database divided patients into four groups according to BNP levels at baseline versus 4 months. They observed that change in BNP over time conveyed independent prognostic information when compared to single determination of BNP. In contrast, Miller *et al*³ attempted to replicate these findings outside the setting of a clinical trial. They followed a cohort of 190 CHF patients and demonstrated that elevation of BNP above normal at any time during follow-up was associated with increased risk of events. However, once elevated, either an increase or decrease, even a decrease to a normal level, was not associated with any further changes in risk level. Recently the 'Trial of intensified versus standard medical therapy in elderly patients with congestive heart failure' (TIME-CHF) investigators⁴ compared BNP guided therapy versus conventional therapy, they noted no difference in overall survival between the two groups however in patients aged <75 years of age the BNP guided therapy group had statistically improved hospital free survival. In the

backdrop of these conflicting findings we decided to review our experience of BNP directed therapy in the management of ambulatory CHF patients presenting to the Veterans Association (VA) cardiomyopathy clinic. The aim of the study was to assess the degree of change in BNP levels between two outpatient values taken from a single CHF patient, and to determine if the percent change between values can predict CHF hospitalisations or death over the next 6-months.

MATERIAL AND METHODS

This protocol was approved by the Institutional Review Board of our hospital. Electronic medical records of patients with stable CHF, who were followed in the CHF clinic between January 2004 and October 2006 were reviewed. Patients were included in the study if they had been seen in the clinic on at least 2 separate occasions at least one month apart with BNP measurements on both visits (termed BNP1 and BNP2), and if they had been deemed clinically stable on both visits by the treating physician. Patients were enrolled more than once if they had subsequent BNPs drawn 6 month after the previous BNP2. Patients excluded from the study if they were hospitalised within one week of their clinic visit, as that was felt to imply that they were not clinically stable when last seen in their clinic visit. Basic demographic information was collected for all patients. Variables recorded during each clinic visit included, BNP level, creatinine level, weight, and last recorded ejection fraction by echocardiography. In our clinic BNP is measured using a commercially available assay (Biosite

Triage, Biosite Inc., San Diego, CA, USA) within 60 minutes after venipuncture.

Information about dosage of the patients' CHF medications, as well as any changes made in dosage were also collected. Patients were divided into two groups, those with >70% increase from baseline BNP, and those in whom the BNP did not increase by greater than 70% of the baseline value or in whom the BNP level decreased. This cut-off was based on an article⁵ which suggested that a greater than 71% week to week change in BNP levels represents a clinically significant change.

Primary outcome measured was the need for hospitalisation for CHF or death within 6 months of the second clinic visit. Since all the patients came to the VA medical centre for their health care needs we do not feel any events were missed. Clinic notes were reviewed for any mention of hospitalisations at outside facilities.

Comparisons were made with unpaired *t*-test for normally distributed data and expressed as Mean±SD. Log rank test was used for non-normally distributed data. Chi-squared analysis or the Fisher exact test, where appropriate were used for categorical parameters. Multivariate regression analysis was performed using a model that included among other variable, change in BNP, absolute BNP, ejection fraction (EF), creatinine, as well as CHF medications in visit one and two. A *p*<0.05 was considered as significant. Statistical analysis was done with SIGMASTAT version 2 statistical software (SPSS Inc. Chicago IL USA).

RESULTS

One hundred and fourteen (114) paired BNP measurements from 62 different patients were included in the study. In 26 cases there was >70% increase from baseline BNP value, whereas in 88 cases the BNP value did not increase more than 70%, or actually decreased. There were no differences between the two groups with regards to baseline co-morbidities, ejection fraction or aetiology of heart failure. Since this was a VA population, all patients were males with a mean age of 74 years. Table-1 describes the CHF medications that both groups were on. Although the majority of patients were on beta blocker (Days and 93% at second visit) and ACE inhibitor/ARB (80% and 74% at second visit) therapy, only a minority of them (<14%) were at target dose for beta blockers and half were at target dose for ACE inhibitor/ARB. As would be expected the majority of patients were on chronic diuretics. The group that demonstrated a significant increase in BNP had a lower BNP1 than the other group (median of 235 versus 429 pg/ml respectively), however there was no major differences in BNP2 values (median of 581 versus 365 pg/ml respectively). There was no statistical difference between the two groups with regards to median time between clinic visits, creatinine or weight.

On univariate analysis, significant change in BNP predicted 6 month mortality or need for CHF hospitalization (Beta estimate 1.04, 95% Confidence Interval 0.446–1.714, *p*<0.01). Other significant predictors of adverse outcomes included worsening EF, chronic renal insufficiency (CRI) and absence of spironolactone use at visit 2.

Table-1: Comparison of CHF therapy between two groups

	Increase in BNP		<i>p</i>
	Significant (n=26)	Not significant (n=88)	
Beta Blockers (BB) (%)			
Taking BB at first visit	23 (88%)	77 (88%)	0.895
On recommended dose at first visit	2 (7.7%)	14 (16%)	0.289
Taking BB at second visit	23 (88%)	81 (92%)	0.570
On recommended dose at second visit	3 (12%)	14 (16%)	0.583
ACE inhibitor/ARB (%)			
Taking ACEi/ARB at first visit	16 (62%)	63 (72%)	0.329
On recommended dose at first visit	11 (42%)	35 (40%)	0.817
Taking ACEi/ARB at second visit	18 (69%)	62 (70%)	0.905
On recommended dose at second visit	8 (31%)	32 (36%)	0.6
Spironolactone (%)			
Taking Spironolactone at first visit	5 (19%)	27 (31%)	0.254
On recommended dose at first visit	5 (19%)	17 (19%)	0.992
Taking Spironolactone at second visit	4 (15%)	32 (36%)	0.549
On recommended dose at second visit	4 (15%)	22 (25%)	0.305
Hydralazine (%)			
Taking hydralazine at first visit	4 (15%)	13 (15%)	0.939
On recommended dose at first visit	1 (3.8%)	3 (3.4%)	0.915
Hydralazine at second visit	5 (19%)	18 (20%)	0.891
On recommended dose at second visit	1 (3.8%)	4 (4.5%)	0.878
Isosorbide Mononitrate (IMN) (%)			
Taking IMN at first visit	10 (38%)	33 (38%)	0.929
On recommended dose at first visit	3 (12%)	13 (15%)	0.671
Taking IMN at second visit	11 (42%)	37 (42%)	0.984
On recommended dose at second visit	3 (12%)	13 (15%)	0.662
On Diuretics at first visit (%)			
	22 (85%)	75 (85%)	0.939
On Diuretics at second visit (%)			
	22 (85%)	74 (84%)	0.942
On Digoxin at first visit (%)			
	16 (62%)	33 (38%)	0.029
On Digoxin at second visit (%)			
	14 (54%)	35 (40%)	0.203

On step-wise multivariate regression analysis significant change in BNP continued to be a predictor of adverse outcomes (Table-2).

Table-2: Multivariate Regression Analysis

Variable	Beta Estimate	<i>p</i>
Significant increase in BNP	1.022	<0.01
Ejection Fraction (EF)	0.04	< 0.01
Chronic Renal Insufficiency (CRI)	1.26	<0.01
Spironolactone use at visit 2	0.881	<0.01
ACE inhibitor/ARB use at visit 2	0.62	0.02

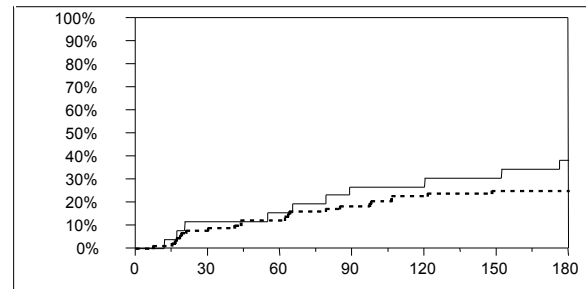


Figure-1: Six month mortality and CHF hospitalisation
 —Significant increase in BNP, - - No significant change in BNP
 *With use of Log Rank test

Figure-1 reveals the hospitalisation for CHF and death rate for both groups 6 months after the last BNP was drawn. The group with a >70% increase in BNP had a significantly greater rate of 6 month CHF hospitalisation or death, using the log rank test ($p=0.04$).

DISCUSSION

Our study reveals that in our cohort of stable CHF patients, percent change in BNP is an independent predictor of 6 month CHF hospitalisation or mortality. This study supports the argument for BNP guided therapy for stable outpatients being managed in a CHF clinic.

Plasma BNP, a neurohormone, is released from cardiac myocytes in response to increased wall stress.⁶ Maisel and colleagues demonstrated that plasma BNP levels are elevated in the setting of an acute exacerbation of CHF.⁷ Since that time there has been a great deal of interest among physicians on the utility of plasma BNP in the outpatient setting. Jourdain and co-workers⁸ randomised patients to receive outpatient care CHF through a BNP guided strategy, aimed at decreasing plasma level to <100 $\mu\text{g/ml}$ versus standard care and noted that the BNP guided group were on significantly higher mean doses of beta-blockers and ACEIs, and at 15 months significantly fewer patients in the BNP group reached the combined endpoint of CHF-related death or hospitalisation. Interestingly 94% of patients in the BNP guided group were at recommended daily dose for ACEIs and 59% were at target dose for beta-blockers at baseline. Although in our cohort 87.7% of patients were on beta-blockers at time of first visit, only 14% were at recommended daily dose. Similarly, only 40.3% of patients were at recommended dose of ACEI/ARB at first visit. These differences exist despite the fact that patients seen in our cohort were followed in a specialised heart failure clinic. This highlights differences in patient tolerability and compliance of medications outside the setting of a clinical trial.

Maeder and co-workers⁹ revealed significant variability in BNP levels in clinically stable CHF patients over a period of a few days. Hence we chose to include BNP levels that had been drawn at least one month apart in clinically stable CHF patients.

In our study we chose to separate the two groups based on a threshold increase of BNP by 70% from clinic visit one to clinic visit two. The reasoning for using a threshold value of 70% was based on an article⁵ which reviewed the intra-individual biologic variances and analytical assay variances of BNP in healthy subjects and stable CHF patients. The author concluded that the week to week BNP reference change value of 71% or greater was clinically significant. Although the article also stated that a lower reference change value was also clinically significant based on different assays, we chose to use 70% as a more

conservative cut off for our analysis. Using the 70% cut-off we did see significantly increased CHF hospitalisations and death in the group that had a >70% increase, and on multivariate regression analysis this variable independently predicted adverse outcomes. We believe this is a forceful argument for using >70% change in BNP as a predictor of adverse outcome that should prompt physicians to make changes in management of patients to prevent hospitalisation. Our results support the conclusions by Latini *et al*² who looked at the Val-HeFT database and noted change in BNP over time was an independent predictor of long term outcomes.

In contrast when the TIME-CHF investigators⁴ randomised 499 patients to a BNP guided therapy arm versus standard medical therapy they did not note a difference in overall clinical outcomes or quality of life. Although like Jourdain *et al*⁸ they too demonstrated that patients in the BNP guided therapy arm were significantly more likely to be at target dose of ACE inhibitors or ARBs and beta-blockers. It is important to note that in their study both groups had a significant reduction in BNP values during the study period, in addition there was an increase in hospital free survival in the BNP guided subgroup of patients who were <75 years of age. It would have been useful to see what the difference in overall health costs was in this subgroup of patients and whether outpatient BNP testing resulted in any cost saving from the decreased hospitalisations.

Strengths of our study are that it demonstrates the value of routine BNP testing outside the setting of a clinical trial, in a 'real world' population. The results suggest the benefit of routine BNP measurements in stable CHF patients. Although it is not clear from this study what intervention(s) would be appropriate in the setting of an increasing BNP level >70% baseline, at the minimum, more frequent follow-up should be done in the presence of a substantial increase in BNP level. This strategy whether accompanied by more aggressive neurohumoral blockade or adjustment of diuretic doses, could reduce hospitalisations and healthcare costs.

Limitations of our study include its retrospective design. In addition we were only able to follow patients for 6 months after BNP2 was drawn making it difficult to interpret the impact of BNP guided maintenance therapy has on long term outcomes. We feel there is a need to create a multi-institutional registry of CHF clinic patients who are followed by a BNP guided approach and compare them to patients in whom BNP is not routinely checked in order to properly gauge the impact this strategy has on patient outcomes and cost of health care. Although this approach was applied by the TIME-CHF investigators, this was done in the setting of a clinical trial and both group of patients had a reduction in BNP levels in their study. The investigators did not report whether there was a difference in

outcomes in those subgroup of patients who had an increase in their BNP values over the course of the study. In addition, if it can be shown that by performing this relatively inexpensive test there is an improvement in hospital free survival then its performance can still be justified even if there is no difference in overall survival.

CONCLUSION

The main finding of our study is that >70% increase in BNP is an independent predictor of CHF hospitalisation or death at 6 months.

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Address for Correspondence:

Dr. Ali S. Wahla, Pulmonary Consultant, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan. **Cell:** +92-308-4444897

Email: alis@skm.org.pk