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# Role of B-type natriuretic peptide (BNP) in heart failure

DOI 10.1515/ijdh-2015-0021

Received September 6, 2015; accepted February 12, 2016; previously published online April 28, 2016

## Abstract

**Introduction:** Early clinical diagnosis of heart failure (HF) is challenging because the signs and symptoms are neither sensitive nor specific for diagnosis. B-type natriuretic peptide (BNP), a cardiac neurohormone is a useful biomarker for patients with HF.

**Objectives:** The purpose of this review is to evaluate the role of BNP in HF as a diagnostic, prognostic, and therapeutic marker in both outpatient care and urgent care settings.

**Methodology:** An extensive literature review was conducted for this study.

**Findings:** Determination of BNP is particularly useful as a rule-out test for suspected cases of HF in patients with dyspnoea. HF is very unlikely in patients with levels of BNP <100 pg/mL whereas BNP levels >400 pg/mL strongly support the diagnosis of HF. Elevated level of BNP indicates a worse prognosis in patients with HF.

**Conclusion:** Although, it is recommended in the diagnostic pathways of guidelines for HF, it is not well established to recommend measurement of BNP to titrate HF medications because of lack of enough evidence. It requires further in-depth research.

**Keywords:** B-type natriuretic peptide; cardiac neurohormone; heart failure; natriuretic peptide; N-terminal B-type natriuretic peptide.

## Introduction

Heart failure (HF) still remains a major challenge especially in the area of clinical diagnosis. This is because the

common symptoms typically associated with HF such as peripheral oedema, shortness of breath, and fatigue, are neither sensitive nor specific for HF. It should also be noted that classically associated signs including crepitation, peripheral oedema, a third-heart sound, and a raised jugular venous pressure are often absent. Echocardiography is generally recognised as the gold standard investigation for detecting the presence of HF. However, it is not always easily accessible and may not always be diagnostic in acute presentation [1]. Furthermore, patients with suspected HF and preserved left ventricular (LV) systolic function may have unremarkable echocardiographic findings [2, 3]. Many studies have now demonstrated that diagnosis of HF is based on history, physical signs, and standard testing may be inadequate [4, 5]. As a result, There is a need for other investigations with high sensitivity and specificity in order to determine the presence or absence of HF especially in the acute setting [6].

The purpose of this review is to evaluate the potential use of B-type natriuretic peptide (BNP) levels in both outpatient care and urgent care settings for the management of HF including its role as a diagnostic, prognostic, and therapeutic monitoring tool.

## B-type natriuretic peptide

BNP is one of a family of structurally similar peptide hormones that includes atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP), and urodilatin. BNP was first isolated from porcine brain in 1988 [7]. In humans, the majority of BNP is formed in ventricular cardiomyocytes. The initial molecule is a 134-amino acid protein, pre-pro-BNP. After cleavage of a signal peptide (26 amino acid), a 108-amino acid pre-hormone, pro-BNP remains. Before release into the blood stream, pro-BNP is cleaved into two parts, the biologically active 32-amino acid chain BNP and the inactive 76-amino acid neurohormone NT-proBNP (N-terminal pro B-type natriuretic peptide) [8]. BNP and NT-proBNP differ with regard to their biological half-life, in vitro stability and mechanisms involved in their clearance [9].

BNP and NT-proBNP are cardiac neurohormones secreted from cardiac myocytes in response to cardiac

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**Table 1:** BNP versus NT-proBNP [10].

| Characteristics                        | BNP                                                                        | NT-proBNP       |
|----------------------------------------|----------------------------------------------------------------------------|-----------------|
| Amino acid                             | 32                                                                         | 76              |
| Molecular weight, kDa                  | 3.5                                                                        | 8.5             |
| Half-life, min                         | 20                                                                         | 120             |
| Clearance mechanism                    | Neutral endopeptidase, natriuretic peptide receptor-C, and renal clearance | Renal clearance |
| Correlation with GFR                   | Moderate                                                                   | Strong          |
| Stability in vitro at room temperature | 4 h                                                                        | Up to 72 h      |
| Biologically active                    | Yes                                                                        | No              |
| Clinical range, pg/mL                  | 0–5000                                                                     | 0–35,000        |

BNP, B-type natriuretic peptide levels; NT-proBNP, N-terminal pro B-type natriuretic peptide.

wall stress caused by pressure or volume overload [10] (Table 1) and its release is triggered by physiological and pathological stimuli [11] (Table 2). The cardiac hormone relaxes vascular smooth muscle and increases capillary permeability [12]. In the kidney, it increases the glomerular filtration, inhibits the release of renin, and reduces sodium reabsorption in the collecting ducts. It also inhibits the release of aldosterone and antidiuretic hormone (ADH), while reducing sympathetic nervous activity. By promoting vasodilatation, natriuresis, and diuresis, BNP reduces preload and afterload [13].

## Methodology

A structured narrative literature review was carried out accessing the following databases: MEDLINE, CINAHL, EMBASE, Google Scholar, Science Direct, Evidence based Medicine Reviews, and the Cochrane Library. The keywords including cardiac neurohormones, natriuretic peptide, BNP, brain natriuretic peptide, NT-proBNP, congestive heart failure (CHF), HF, diagnosis, prognosis, treatment, and combination of the key terms were used to search the literature. The search was restricted to trials on humans published in or translated into English between 1985 and August 2011. The articles were preferentially selected using the following inclusion criteria:

**Table 2:** Causes of raised B-type natriuretic peptide levels (BNP) [11].

|                                           |                                                                              |
|-------------------------------------------|------------------------------------------------------------------------------|
| 1. Congestive heart failure               | 6. Other cardiac conditions (e.g. cardiac tamponade, valvular heart disease) |
| 2. Left ventricular systolic dysfunction  | 7. Pulmonary embolism                                                        |
| 3. Left ventricular diastolic dysfunction | 8. Renal dysfunction                                                         |
| 4. Left ventricular hypertrophy           | 9. Advanced age                                                              |
| 5. Atrial fibrillation                    |                                                                              |

1. Randomized, blinded, controlled studies, and well-designed cohort studies.
2. Trials included a standard reference, such as echocardiography, to diagnose HF.

## Findings

### Role of BNP as a diagnostic biomarker

There are many randomised trials and systemic reviews conducted over a decade to research the potential value of BNP for diagnosis of HF. The following trials were performed in different clinical settings to examine the impact of BNP/NT-proBNP to rule in or rule out HF.

### Role of BNP in urgent care and emergency departments

Dao et al. evaluated the utility of BNP in the diagnosis of CHF [14]. At a blood concentration of 80 pg/mL, BNP was an accurate predictor of the presence of CHF (95%); measurements less than this had a high negative predictive value (98%). The measurement of BNP appears to be a sensitive and specific test to diagnose CHF in urgent care settings. The largest study of the diagnostic utility of BNP is the Breathing Not Properly Multinational Study (BNPMS) or (BNP Multinational study) [15]. The diagnostic accuracy of BNP at a cutoff of 100 pg/mL was 83.4%. The negative predictive value of BNP with a cutoff point of 50 pg/mL was 96%. McCullough et al. further analysed the BNPMS data and stated that CHF is unlikely with BNP level <100 pg/mL, possible with levels between 100 and 500 pg/mL and probable at levels >500 pg/mL [16].

Lainchbury et al. compared the utility of measurement of BNP and NT-proBNP in the diagnosis of HF in patients with acute dyspnea [17]. Results of this study support the use of BNP and NT-proBNP measurement in the assessment of patients presenting to hospital with shortness of breath. The ProBNP investigation of Dyspnea in the Emergency Department (PRIDE) study is the largest trial to date to definitely establish the role of NT-proBNP testing for diagnosis of acute CHF in emergency settings [18]. NT-proBNP testing alone was superior to clinical judgment for diagnosing acute HF; NT-proBNP plus clinical judgment was superior to NT-proBNP or clinical judgment alone. NT-proBNP measurement is a valuable addition to standard clinical assessment for the identification and exclusion of acute CHF in the emergency department setting.

In the 2009 ACCF/AHA heart failure guidelines [19], Jessup et al. suggest that measurement of natriuretic

peptides (i.e. BNP and NT-proBNP) can be useful in evaluation of patients in an urgent care setting in whom the clinical diagnosis of HF is uncertain. In the current ESC guidelines [20] (Table 3) for the management of HF, Dickstein et al. for the first time introduced BNPs as diagnostic tools for patients with symptoms suggestive of HF. According to the ESC recommendation, chronic HF is unlikely if there is BNP < 100 pg/mL and NT-proBNP < 400 pg/mL and HF is likely if BNP > 400 pg/mL and NT-proBNP > 2000 pg/mL. Diagnosis is uncertain in case of BNP 100–400 pg/mL and NT-proBNP 400–2000 pg/mL. The NICE guidelines development group recommends the following thresholds [21] (Table 3):

1. BNP > 400 pg/mL or NT-proBNP > 2000 pg/mL: patient should have an echocardiography and specialist clinical assessment within 2 weeks from the time of presentation.
2. BNP 100–400 pg/mL or NT-proBNP 400–2000 pg/mL: patient should have echocardiography and clinical assessment by the specialist within 6 weeks from the time of presentation.
3. BNP < 100 pg/mL or NT-proBNP < 400 pg/mL, in the absence of HF therapy: HF is an unlikely cause for the presentation.

Mant et al. confirmed in the systematic review [22] that ECG, BNP, and NT-proBNP all have high sensitivities (89%, 93%, and 93%, respectively) (Table 4). A chest X-ray is moderately specific (76%–83%) but insensitive

(67%–68%). BNP was found to be more accurate than ECG, with a relative diagnostic odds ratio of ECG/BNP of 0.32 [95% confidence interval (CI) 0.12–0.87]. BNP plus clinical features performed better than ECG plus clinical features. Several studies compared the diagnostic accuracy of BNP with that of NT-proBNP for the clinical diagnosis of HF and revealed that there was no statistical difference in the diagnostic accuracy between the two tests [23, 24]. Some authors, however, have recently stated that NT-proBNP appears superior to BNP for the evaluation of suspected acute HF with preserved LV ejection fraction (LVEF) [25].

### Use of BNP in primary care

The Natriuretic Peptides in the Community Study determine the effect of NT-proBNP on the accuracy of HF diagnosis in primary care [26] and shows that availability of NT-proBNP measurement to general practitioners (GPs) significantly improves the diagnostic accuracy of HF in primary care by decreasing over diagnosis of HF. Hill et al. conducted a systematic review of randomized control trials and observational studies to determine the screening and diagnostic properties of BNP and NT-proBNP for HF in primary care. This systemic review demonstrated that there is insufficient evidence to support the use of the natriuretic peptides to screen general asymptomatic populations for HF. However, NT-proBNP performed marginally

**Table 3:** Cut points of BNP/NT-pro BNP recommended by guidelines [19–21].

| Guidelines | HF unlikely                                              | HF likely                                                                                   | HF uncertain                                                                                    |
|------------|----------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| ESC        | BNP < 100 pg/mL<br>NT-proBNP < 400 pg/mL                 | BNP > 400 pg/mL<br>NT-proBNP > 2000 pg/mL                                                   | BNP 100–400 pg/mL<br>NT-proBNP 400–2000 pg/mL                                                   |
| NICE       | BNP < 100 pg/mL<br>NT-proBNP < 400 pg/mL                 | BNP > 400 pg/mL<br>NT-proBNP > 2000 pg/mL<br>Need echocardiogram<br>and clinical assessment | BNP 100–400 pg/mL<br>NT-proBNP 400–2000 pg/mL<br>Need echocardiogram and<br>clinical assessment |
| ACC/AHA    | There is no recommended cut off values for BNP/NT-proBNP |                                                                                             |                                                                                                 |

BNP, B-type natriuretic peptide levels; NT-proBNP, N-terminal pro B-type natriuretic peptide; HF, heart failure.

**Table 4:** Overall accuracy of investigations of heart failure [22].

| Characteristics                     | No. of patients | Sensitivity | Specificity | Youden index |
|-------------------------------------|-----------------|-------------|-------------|--------------|
| ECG                                 | 4702            | 89          | 56          | 45           |
| CXR: any abnormality                | 2323            | 68          | 83          | 51           |
| CXR: increased cardiothoracic ratio | 2797            | 67          | 76          | 43           |
| BNP                                 | 4744            | 93          | 74          | 67           |
| NT-proBNP                           | 4229            | 93          | 65          | 58           |

BNP, B-type natriuretic peptide levels; NT-proBNP, N-terminal pro B-type natriuretic peptide.

better than BNP when used for screening asymptomatic at-risk populations [27, 28].

## BNP as a prognostic biomarker in HF patients

There are several studies performed to evaluate prognostic significance of natriuretic peptide. The predictive value of BNP/NT-proBNP was evaluated in the following trials of large cohort of patients with symptoms of HF.

### Prognostic value in patients with LV systolic dysfunction

In a larger study of 452 patients with LVEF <35%, Berger et al. found that BNP levels were a strong independent predictor of sudden death [29]. The prospective Copenhagen Hospital Heart Failure (CHHF) study showed that measurements of NT-proBNP add additional prognostic information independent of LVEF, and is a strong predictor of 1-year mortality in hospitalized patients with HF regardless of systolic dysfunction [30]. The COPENICUS NT-proBNP substudy investigated the prognostic value of NT-proBNP in a large number of patients with severe CHF. NT-proBNP was consistently associated with increased risk for all-cause mortality and or hospitalization for HF in patients with severe CHF [31].

There is a strong association between admission BNP level and in hospital mortality irrespective of ejection fraction [32]. BNP at admission in the emergency department is also powerfully associated with cardiovascular hospitalizations at 90 days [33]. However, discharge BNP level is more useful for long-term prognostication. Measurement of natriuretic peptide at discharge has been shown to predict hospital readmission or death for at least 6 months for decompensated HF [34, 35]. Furthermore, it has been suggested that the change in natriuretic peptides during hospitalization is the strongest predictor of adverse outcome with increasing levels during admission being associated with poor prognosis and decreasing levels with better prognosis.

### Prognostic value in patients with chronic HF and preserved LV systolic function

Some studies have shown similar mortality and hospital readmission rates among HF patients with preserved LV systolic function as compared to HF patients with reduced systolic function [36, 37] while others describe a more benign prognosis for patients with preserved systolic function [38, 39]. NT-proBNP increases with the severity of

ventricular systolic as well as diastolic dysfunction [40–42]. The results of CHHF study [29] have shown that measurement of NT-proBNP level is useful to predict the probability of death within 12 months after hospital admission in patients with systolic dysfunction as well as in those with preserved systolic function. Similarly, NT-proBNP values at discharge or changes in NT-proBNP concentration during hospitalization are useful to identify patients at risk of adverse outcomes regardless of systolic function [43].

Although some studies have shown the promising results of the BNP/NT-proBNP assay in patients with chronic HF and preserved LV systolic function for the prediction of adverse cardiovascular incidence, its prognostic value is still not well established because there are scarce evidence in this group of patients.

## Role of BNP in the management of HF

The concept of titrating HF treatment to achieve a target level of BNP was first investigated by Troughton et al. in a small study, which showed borderline beneficial results in those patients receiving BNP guided therapy [44]. Later on, TIME-CHF and BATTLESCARRED prospectively addressed the efficacy of a biomarker-guided strategy in older patients compared to younger patients and proved that NT-proBNP guided management improved clinical outcomes in patients aged <75 years but not in those above 75 years of age [45, 46]. The PRIMA (can pro-brain-natriuretic peptide guided therapy of chronic heart failure improve heart failure morbidity and mortality?) study also demonstrated that in the NT-proBNP guided group, mortality was lower compared to the clinically guided group, but this was not statistically significant ( $p=0.206$ ). However, an improved outcome was seen in patients <75 years of age [47].

Felker et al. performed a quantitative meta-analysis of available randomized controlled trials to evaluate the impact of biomarker-guided therapy on mortality in patients with chronic HF [48]. The primary finding of this meta-analysis is that titration of chronic medical therapy based on serial measurement of natriuretic peptides is superior to control strategies, with an approximately 30% reduction in the risk of all-cause mortality. A recent meta-analysis conducted by Porapakkham et al. revealed a significant decline of all-cause mortality in people younger than 75 years, which is identical to the results of trials mentioned above [49].

At present, there are too few data available to make a firm recommendation regarding target BNP levels and levels at which treatment should be altered. However, rising BNP concentrations alert the clinician regarding

the deterioration of HF. It is not yet clear how frequently natriuretic peptide levels should be measured and whether it is better to treat to a target BNP level or to reduce BNP level by specific percentage.

## Discussion

On the basis of current evidence, measurement of plasma BNP is of most value in the diagnostic arena where it is likely to improve the performance of nonspecialist clinicians to differentiate patients with dyspnoea due to CHF from those with dyspnoea due to other noncardiac causes. In clinical practice, BNP testing is best used as a 'rule out' test for suspected cases of new HF in breathless patients presenting to either the outpatient or emergency care settings. However, it is not a replacement for echocardiography and full cardiological assessment, which will be required for patients with an elevated BNP concentration. In patients with dyspnoea, a low concentration of BNP can accurately rule out decompensated HF, whereas a very high concentration of this peptide clearly supports the diagnosis of HF but does not exclude presence of other diseases contributing to dyspnoea. BNP is less accurate as a general screening test for detecting cardiac structural abnormalities in patients who are asymptomatic than in those with symptoms, but might be helpful in selected populations at high risk. The potential value of BNP/NT-proBNP has recently been recognized by their inclusion in the recent European and NICE guidelines for diagnosis of HF. Though several small studies show that NT-proBNP measurement may have an advantage over BNP in the diagnosis of early stage HF or asymptomatic LV dysfunction because of its longer half-life, there is no significant statistical difference in the diagnostic performance of these two tests.

The BNP/NT-proBNP is a useful investigation to predict outcomes in patients with HF. Several randomized control trials evaluated prognostic value of BNP and confirmed its potential role to predict prognosis of HF patients. High levels of BNP/NT-proBNP are associated with worse prognosis in patients with decompensated HF. BNP is an independent predictor of cardiovascular mortality or hospitalization for HF in patients irrespective of LVEF, NYHA functional class and age. Serial measurement of NT-proBNP levels can identify high-risk patients who might need intensification of therapy or closer monitoring and help with discharge planning. However, prognostic value of biomarkers in HF with preserved systolic function or diastolic HF is not well supported despite promising results of the BNP/NT-proBNP measurements demonstrated by a number of trials. In head-to-head comparison,

NT-proBNP is slightly superior to BNP for predicting death and morbidity or rehospitalization for HF.

Optimizing medical therapy for individual patients remains one of the major challenges of HF management. Several studies had been conducted on these premises to titrate the antifailure medications according to BNP/NT-proBNP levels and demonstrated that BNP-guided therapy are promising especially in younger patients. A recent meta-analysis had revealed the beneficial effects of BNP-guided therapy in patients under the age of 75 years only. Much of the benefit from this approach is likely due to intensive drug therapy. Still there is no guideline recommendation to titrate doses of HF drugs according to BNP measurement because of lack of firm evidences on BNP guided management.

## Conclusion

Presently BNP/NT-proBNP is recognized as a potential biomarker in ruling out HF in multiple clinical settings and is recommended in the diagnostic pathways of national and international guidelines for detection of HF. Measurements of plasma BNP/NT-proBNP concentrations provide important prognostic information on cardiovascular mortality and morbidity in patients with HF regardless of ejection fraction, NYHA functional class and gender. Optimization of medical therapy for HF based on plasma BNP level is proven to be beneficial only in patients <75 years old. However, there is no firm evidence to suggest routine measurement of natriuretic peptide can guide therapeutic strategies. Further research is needed to determine whether BNP guided therapy is useful in patients over the age of 75 years.

**Acknowledgements:** Professor Andrew Owen supported in generating ideas for the dissertation and consented to act as a supervisor for this study.

**Research funding:** This work was supported personally by the author without funding from any organization or institute and conducted as part of MSc in the cardiology programme of Canterbury Christ Church University, UK.

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

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