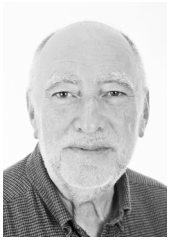
Natriuretic peptide measurement in heart failure

October 2017



Chris Higgins
Little Acre, Main Road
Shurdington
Nr Cheltenham
Gloucester
GL51 4XF, UK
E-mail: cjhiggins@hotmail.co.uk

Summary

This paper is an up-to-date account of research and current clinical practice guideline recommendations. Chris Higgins summarizes the recommendations of 2 new guidance documents on the use of natriuretic peptides in heart failure. The first document is a systematic review of published research (up to 2016) on the role of biomarkers (including natriuretic peptides) in heart failure conducted by an expert group on behalf of the American Heart Association (AHA). The second document is the 2017 update of 2013 American College of Cardiology (ACC)/AHA Guideline for Management of Heart Failure. The article begins with brief overviews of BNP/NT-proBNP and heart failure.

Measurement of circulating natriuretic peptide (either BNP or NT-proBNP) concentration has been a routine part of the clinical assessment of patients with suspected heart failure for close to 15 years following discovery that heart failure is associated with increased concentration of both peptides. Voluminous research over this 15-year period has sought to refine and extend the clinical utility of the two tests and allow evidence-based guidelines for their clinical use in heart failure.

The focus of, and impetus for this article is two recently published, potentially influential papers [1, 2]. Together they provide current group expert view of the value (and limitations) of BNP, NT-proBNP testing in heart failure. The first [1] is a systematic review of published research (up

to 2016) on the role of biomarkers (including natriuretic peptides) in heart failure conducted by an expert group on behalf of the American Heart Association (AHA).

The second [2] is the 2017 update of 2013 American College of Cardiology (ACC)/AHA Guideline for Management of Heart Failure. By way of introduction to discussion of the content of these two papers, the article begins with brief overviews of BNP/NT-proBNP and heart failure.

Natriuretic peptide (BNP and NT-proBNP) overview

Brain or B-type natriuretic peptide (BNP) was first isolated from pig brain in 1988 [3]. Three years later it was demonstrated that human BNP is derived principally from heart muscle cells (myocytes) that comprise the walls of the ventricles of the heart. BNP is a cardiac hormone released to the circulation from ventricular myocytes in response to ventricular wall stretch/stress caused by pressure and volume overload.

The cardiovascular protective hormonal effects of BNP include: increased urinary excretion of water and sodium (diuresis and natriuresis); vasodilation; and inhibition of the renin-angiotensin-aldosterone (RAAS) system. These effects imply a pivotal physiological role for BNP in control of blood pressure and intravascular volume during cardiovascular stress [4].

Release of BNP to the circulation from ventricular myocytes is a process. The BNP gene encodes a much larger precursor molecule called pre-proBNP which is enzymatically cleaved to produce the inactive pro-hormone (pro-BNP), comprising 108 amino acids. Further enzymatic cleavage of pro-BNP results in release of two peptides to the circulation: the active hormone BNP comprising 32 amino acids; and the remaining N(amino)-terminal section of pro-BNP (NT-proBNP), comprising 76 amino acids.

Unlike BNP, NT-proBNP has no known physiological function. But as a biomarker of ventricular stretch/stress, NT-proBNP is equal to BNP. The two blood tests are equally valid for clinical purposes [5, 17]. Although released in equimolar amounts, their differing half-life in the circulation (BNP 20 mins, NT-proBNP 120 mins) determines that NT-proBNP values can be approximately six times higher than BNP values [6].

Heart failure overview

Heart failure (HF) is a common chronic condition, which predominantly affects the elderly. Prevalence is 0.8-2% in the general population but 10-20% among those aged >70 years [7]. With an ever-ageing population, prevalence is increasing. In the US, HF currently affects 5.8 million; one estimate predicts that this will rise to more than 8 million by 2030 [8].

HF is a complex syndrome with many possible causes that result from impaired ability of the left ventricle to either fill with blood during the diastolic phase of the cardiac cycle or eject blood during the systolic phase of the cardiac cycle. The affected heart is consequently increasingly less able to pump a sufficient blood volume to meet the oxygen demands of the body. Heart imaging (echocardiography) allows measurement of the left ventricular ejection fraction (LVEF).

This is the % of the total blood volume in the left ventricle that is ejected during systole and is normally around 50-70%. HF due to impaired ventricular ejection is associated with reduced ejection fraction (rEF), i.e. <50% and is referred to as HFrEF or systolic heart failure. HF due to impaired ventricle filling is associated with preserved EF (i.e. >55%) and is referred to as HFpEF or diastolic heart failure. Heart imaging allows detection of left ventricular dysfunction (either systolic or diastolic) before symptoms of heart failure occur.

Previous myocardial infarction (MI) and chronic hypertension (CH) are the two most common

causes of HF. Diabetes is associated with increased risk of HF, independent of previous MI or chronic hypertension.

Cardinal symptoms of HF include: breathlessness after only mild exertion (dyspnea); exercise intolerance, fatigue; and eventually ankle swelling/pain due to local fluid (edema) accumulation. HF is a progressively debilitating condition. The New York Heart Association (NYHA) Functional Classification [9] is widely used to classify the severity of HF to one of four classes based on the extent to which physical activity is limited.

NYHA Class I is essentially asymptomatic HF, and NYHA Class IV is applied to patients with most severe HF who are "unable to carry on any physical activity without discomfort". These Class IV HF patients "experience symptoms (breathlessness, fatigue, etc.) at rest".

Typically, patients have periods of chronic stable HF, punctuated by acute exacerbation, called acute (decompensated) heart failure (AHF) when symptoms and hemodynamic condition worsen significantly, requiring emergency admission to hospital. AHF, which may occur in those who have not yet been diagnosed with HF, is associated with high mortality. Around 12-15% of patients hospitalized for AHF die within 12 weeks, and 30% die within 12 month of admission [10].

Increased ventricle wall stretch/stress is a feature of heart failure that accounts, at least in part, for the increased release to the circulation of natriuretic peptides BNP and NT-proBNP.

Content of the two highlighted papers [1, 2]

Research on the clinical value of BNP/NT-proBNP in HF (summarized in [1]) can be addressed under four headings:

- Predicting risk of HF (and thereby preventing HF)
- Diagnosis of HF
- Determining severity of HF and prognosis for patients with HF and AHF
- Guiding HF therapy

Predicting risk of HF

The notion that measurement of BNP or NT-proBNP among those without HF could be used to help predict their risk of future HF has only recently been confirmed by the results of studies published in the past 7 years [11-15]. Two randomized trials [16, 17] suggest that early treatment of those identified at high risk of HF on the basis of BNP/NT-proBNP testing may prevent or delay onset of HF.

The 2017 update guideline task force [2] recommend the use of BNP/NT-proBNP testing to screen for HF among those at high risk. They state that this screening followed by early intervention may prevent HF. This is a Class IIa (moderate strength) recommendation based on evidence judged to be of moderate quality (Level B-R).

Diagnosis of HF

BNP and NT-proBNP are the best-established and best-evaluated markers to help in the proper diagnosis and exclusion of HF [1].

Numerous studies have investigated the value of BNP and NT-proBNP to aid diagnosis of HF; two large meta-analyses [18, 19] summarized this data. These convincingly demonstrate that these blood tests improve diagnosis (compared with clinical assessment alone) of HF, AHF (and asymptomatic left ventricular dysfunction) in both primary care and hospital emergency room settings [1].

The most widely used diagnostic application of BNP/NT-proBNP is investigation of patients with dyspnea, the most common (but non-specific) symptom of heart failure [1]. A landmark study published in 2002 [20] was influential in this regard. This multinational study of 1586 emergency room patients presenting with acute dyspnea

determined that using a cut-off BNP value of 100 pg/mL, the test accurately diagnoses HF with a sensitivity of 90% and specificity of 70%.

A subsequent similarly designed study [21] found that an NT-proBNP level of less than 300 pg/mL was optimal for ruling out HF (negative predictive value 99%). These and other studies led to the now widely used cut-off values to exclude a diagnosis of acute heart failure (AHF).

A diagnosis of AHF is unlikely if:

BNP is <100 pg/mL
or NT-proBNP is <300 pg/mL

The relatively low specificity for HF at "the rule out HF" cut-off values defined in these studies highlights the fact that HF is increased in a number of non-HF conditions (both cardiac and non-cardiac) listed in Table I.

Higher than expected BNP/NT-proBNP values	Lower than expected BNP/NT-proBNP values
Acute coronary syndrome	Obesity
Renal Insufficiency	Flash pulmonary edema
Right ventricular dysfunction	Pericarditis/ tamponade
Atrial Fibrillation	End-stage cardiomyopathy
Pulmonary hypertension	
Pulmonary embolism	
Anemia	
Sepsis	
Mitral regurgitation	
Advanced ageing	

TABLE I: Non-heart failure factors that affect BNP/NT-proBNP values [1]

Higher cut-off values (with high specificity and positive predictive value for HF) are consequently needed to reliably rule in a diagnosis of HF. Study has revealed the following recommended values [22].

A diagnosis of HF is supported if:

BNP is >400 pg/mL
or if NT-proBNP is >450 pg/mL for those less than 50 yrs
>900 pg/mL for those 50-75 yrs
>1800 pg/mL for those >75 yrs

BNP/NT-proBNP values in the grey zone between rule out HF and rule in HF (e.g. BNP 100-400 pg/mL) pose a diagnostic dilemma [1]. They could indicate left ventricular dysfunction or mild HF but due consideration should also be given to the possibility of non-HF conditions listed in Table I. Obesity is associated with reduced BNP/NT-proBNP values and so represents another confounding factor for interpretation of test results [23].

The 2017 update guideline task force [2] recommend the use of BNP/NT-proBNP to make or exclude a diagnosis of HF in patients presenting with dyspnea either in the community or emergency room setting. This is a Class 1 (highest strength) recommendation based on evidence judged to be highest quality (A).

They caution that clinicians should be aware that elevated levels have been associated with both cardiac and non-cardiac disease. The task force do not recommend particular BNP/NT-proBNP values that should be used to either make or exclude a diagnosis of heart failure.

Determining severity of HF and prognosis for patients with HF and AHF

A number of studies have established that BNP and NT-proBNP values parallel severity of HF assessed by NYHA functional classification as well as imaging measures of cardiac dysfunction in HF [1].

Generally, the higher the value the more severe is the HF. High values are suggestive of worse clinical outcomes and higher risk of death [1]. Analysis of pooled data from 32 studies examining the prognostic value of BNP demonstrated that each 100 pg/mL increase in BNP was associated with 35% increase in relative risk of death [24].

A study of 48,629 AF patients [25] confirmed that BNP at hospital admission for acute decompensated HF is independently predictive of in-hospital mortality for those with either reduced or preserved LVEF (i.e. HFrEF or HFpEF). In this study 1.9% of patients whose admission BNP was in the lowest quartile (<430 pg/mL) died before discharge from hospital, compared with 6% among those whose admission BNP was in the highest quartile (≥1730 pg/mL).

Likewise, admission NT-proBNP is also strongly predictive of outcome for patients admitted to hospital with acute decompensated HF. Januzzi *et al*. [26] identified a hospital admission NT-proBNP level of >986 pg/mL as the strongest predictor of 1-year mortality. In their study cohort 1-year mortality rate was 29% among AHF patients whose admission NT-proBNP was >986 pg/mL, compared with 0% among those whose admission NT-proBNP was <986 pg/mL.

Both BNP and NT-proBNP levels improve with treatment during HF hospitalization and predischarge values rather than admission values are the best predictor of long-term outcome for those who survive to discharge [1].

A study of 156 AHF patients [27] who survived to discharge from hospital revealed that the risk of death or hospital readmission during the 6 months after discharge was higher for those who did not have a significant reduction (defined as >30%) in NT-proBNP during hospital admission compared with those who did (HR, 2.03, 95% CI, 1.14-3.64) The risk was even higher for those who had a 30% increase in NT-proBNP compared with those who had 30% decrease (HR 5.69; 95% CI, 3.23-11.01).

The 2017 update guideline task force [2] recommend the use of BNP or NT-proBNP to help establish prognosis or disease severity in chronic HF. They also recommend that admission (baseline) BNP or NT-proBNP values be used to establish prognosis for patients hospitalized because of decompensated AHF.

Both are Class 1 (highest strength) recommendations based on evidence judged to be of highest quality (Level A). The task force also state that for all hospitalized HF patients predischarge BNP or NT-proBNP value can be useful to establish postdischarge prognosis. This is a Class IIa (moderate strength) recommendation based on evidence judged to be of moderate quality (Level B-NR).

Guiding HF therapy

Unequivocal evidence that BNP and NT-proBNP levels correlate with severity of HF (both HFrEF and HFpEF) and effective (symptom relieving) drug treatment is associated with declining values continues to drive research interest in the notion that serial BNP/NT-proBNP measurement could be used to guide HF drug therapy, and thereby tailor treatment to the individual patient.

The first randomized trial to test whether such an approach is beneficial was conducted in 2000 [28]. Sixty-nine patients were randomized to either drug dose guided by conventional clinical (symptom) assessment or to drug dose guided by conventional clinical assessment plus NT-proBNP measurement. For those in this second arm of the trial, treatment was adjusted to drive NT-proBNP values below 1700 pg/mL. Those receiving NT-proBNP-guided therapy fared better than those treated conventionally.

During 10 months of follow-up, total cardiovascular events (death, hospital admission or heart failure decompensation) were more common in the conventionally treated group than the NT-proBNP-

guided treatment group (54 vs. 19). Death was higher in the conventionally treated group (7 vs. 1) although this difference did not reach statistical significance.

The positive results of this small early trial led to many more which are discussed in some detail by Cowie *et al*. [1]. In essence, results of subsequent randomized trials have been conflicting; some have suggested, like the original one [28] that BNP- or NT-proBNP-guided treatment is beneficial and some suggest that the strategy is neutral (has no benefit). This is clearly an area of continuing research interest but at the present time there is insufficient data to support BNP-/NT-proBNP-guided HF therapy [1].

The 2017 update guideline task force [2] make no recommendation regarding the use of BNP/NT-proBNP testing to guide HF therapy. In the preamble of their document they state that this is because of the absence of clear and consistent evidence that BNP-/NT-proBNP-guided therapy improves mortality and cardiovascular outcomes.

References

1. Chow C, Maisel A, Anand I *et al*. Role of biomarkers for the prevention, assessment and management of heart failure. Circulation 2017; 135: e1054-e1091
2. Yancy C, Jessup M, Bozkurt B *et al*. 2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA Guideline for the management of heart failure. J Am Coll Cardiol 2017; doi: 10.1016/j.jacc.2017.04.025
3. Sudoh T, Kangawa K, Minamino N *et al*. A new natriuretic peptide in porcine brain. Nature 1988; 332: 78-81
4. Volpe M. Natriuretic peptides and cardio-renal disease. Int J Cardiology 2014; 176: 630-39
5. Masson S, Latini R, Anand I *et al*. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal pro-BNP in a large population of patients with chronic and symptomatic heart failure: the valsarton heart failure (Val-HeFT) data. Clin Chem 2006; 52: 1528-38.
6. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart 2008; 92: 842-49
7. McMurray J, Adamopolous S, Anker S *et al*. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart Journal 2012; 33: 1787-1847
8. Hernandez A. Preventing heart failure JAMA 2013; 310: 44-45
9. Criteria Committee of the New York Heart Association. Nomenclature and Criteria for diagnosis of disease of the heart and great vessels. 9th Ed Boston: Little Brown & Co 1994; 253-56
10. Passantino A, Montillo F, Iacoviello M. Predicting mortality in patients with acute heart failure: role of risk scores. World J Cardiology 2015; 7: 902-11

11. Velagaleti R, Gona P, Larson M *et al*. Multimarker approach for the prediction of heart failure incidence in the community. Circulation 2010; 122: 1700-06

12. Glick D, DeFeilippi C, Christenson R *et al*. Long-term trajectory of two unique cardiac biomarkers and subsequent left ventricular structural pathology and risk of incident failure in community-dwelling older adults at low baseline risk. JACC:Heart Failure 2013; 1: 353-60

13. Wannamethee S, Welsh P, Whincup P *et al*. N-terminal pro brain natriuretic peptide but not copeptin improves prediction of heart failure over other routine clinical risk parameters in older men with and without cardiovascular disease: population-based study. Eur J Heart Fail 2014; 16: 25-32

14. Wang T, Wollert K, Larson M *et al*. Prognostic utility of novel biomarkers of cardiovascular stress: the Framingham Heart Study. Circulation 2012; 126: 1596-1604

15. Smith J, Newton-Cheu C, Almgren P *et al*. Assessment of conventional cardiovascular risk factors and multiple biomarkers for the prediction of incident heart failure and atrial fibrillation. J Am Coll Cardiol 2010; 56: 1712-19

16. Ledwidge M, Gallagher J, Conlon C *et al*. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA 2013; 310: 66-74

17. Huelsman M, Neuhold S, Resl M *et al*. PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. J Am Coll Cardiol 2013; 62: 1365

18. Mant J, Doust J, Roalf A *et al*. Systematic review and individual patient data meta-analysis of diagnosis of heart failure with modelling of implications of different diagnostic strategies in primary care. Health Technol Assess 2009; 13: 1-207

19. Ewals B, Ewald D, Thakkinstian A *et al*. Meta-analysis of B-type natriuretic peptide and N-terminal pro B natriuretic peptide in the diagnosis of clinical heart failure and population screening for left ventricular systolic dysfunction. Internal Med J 2008; 38: 101-13

20. Maisel A, Krishnaswamy P, Novak R *et al*. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. NEJM 2002; 347: 161-67

21. Januzzi J, Camargo C, Anwaruddin S *et al*. The N-terminal ProBNP Investigation of Dyspnea in the Emergency department (PRIDE) study. Am J Cardiol 2005; 95: 948-54

22. Maisel A, Mueller C, Adams K *et al*. State of the art: using natriuretic peptide levels in clinical practice. Eur J Heart Failure 2008; 10: 824-39

23. Madamanchi C, Alhosani H, Sumida A *et al*. Obesity and natriuretic peptides, BNP and NT-proBNP: mechanisms and diagnostic implications for heart failure. Int J Cardiol 2014; 176: 611-17

24. Doust J, Pietrzak E, Dobson A *et al*. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure. BMJ 2005; 330: 625

25. Fonarrow G, Peacock W, Phillips C *et al*. Admission B-type natriuretic peptide level and In-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 2007; 49: 1943-50

26. Januzzi J, Sakhuja R, O'Donaghue M *et al*. Utility of amino terminal pro-brain natriuretic peptide testing for predicition of 1 year mortality in patients with dyspnea treated in the emergency department. Arch Intern Med 2006; 166: 315-20

27. Bettencourt P, Azavedo A, Pimento J *et al*. N-terminal-pro-brain natriuretic peptide predicts predicts outcome after hospital discharge in heart failure patients. Circulation 2004; 110: 2168-74

28. Troughton R, Frampton C, Yandle T *et al*. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000; 355: 1126-30