

Guidelines Review

National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Guidelines on the Clinical Utilization and Analytical Issues for Cardiac Biomarker Testing in Heart Failure

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Over recent years considerable knowledge has accumulated on the clinical utilisation of the B-type natriuretic peptide (BNP) and its co-metabolite N-terminal proB-type natriuretic peptide (NT-proBNP) in the context of heart failure (HF). In July 2007 recommendations were published by the NACB on the clinical utilisation and analytical issues of these biochemical markers of HF.^{1,2} The latter document was a joint effort between the NACB and the International Federation of Clinical Chemistry Committee on Standardisation of Markers of Cardiac Damage.² These two articles provide a good summary of the current state of knowledge and understanding of the BNP and NT-proBNP assays.

This review of the Guidelines focuses mainly on the use of these biomarkers in diagnosis, risk stratification, guiding management of HF and briefly mentions analytical issues covered in the second article.

For a relatively new clinical biochemistry test, an impressive evidence-base has been accumulated from multiple randomised clinical trials and well conducted cohort studies of large numbers of patients. This evidence shows that BNP and NT-proBNP improve the diagnostic accuracy for the detection of HF in patients presenting to emergency departments with dyspnoea. The higher the value, the greater the likelihood that dyspnoea is due to HF. The Table lists the level of evidence provided in the Guidelines and ranges from the best available evidence (class I, level A) to the weakest evidence (class III, level C).³

The NACB Guidelines begin with a brief outline of the definition of HF and the physiology of BNP synthesis followed by recommendations for the use of BNP and NT-proBNP.¹ I have listed each of the recommendations from the article along with the level of evidence supporting the Guideline followed by a brief comment.

I. Recommendations for Use of Biochemical Markers for Diagnosis of HF

Class I: Level of Evidence: A

1. BNP or NT-proBNP testing can be used in the acute setting to rule out or to confirm the diagnosis of heart failure among patients presenting with ambiguous signs and symptoms.

Class IIa: Level of Evidence: C

1. BNP and NT-proBNP testing can be helpful to exclude the diagnosis of heart failure among patients with signs and symptoms suspicious of heart failure in the non-acute setting.

Class III: Level of Evidence: C

1. In diagnosing patients with heart failure, routine blood BNP or NT-proBNP testing for patients with an obvious clinical diagnosis of heart failure is not recommended.

2. In diagnosing patients with heart failure, blood BNP or NT-proBNP testing should not be used to replace conventional clinical evaluation or assessment of the degree of left ventricular structural or functional abnormalities (e.g. echocardiography, invasive haemodynamic assessment).

Comment on the Use of Biochemical Markers for Diagnosis of HF

The Breathing-Not-Properly Study demonstrated that a BNP cut-off of 100 ng/L gave a sensitivity of 90% and a specificity of 76% for the correct diagnosis of HF in emergency department patients presenting with acute dyspnoea.⁴ BNP results, together with the clinical assessment, were superior to clinical assessment alone in determining the cause of acute dyspnoea and also reduced the time to discharge and the total cost of treatment.⁵ Similar findings were reported for NT-proBNP by the PRIDE Study, where cut-off for NT-proBNP of >450 ng/L for ages <50 years and >900 ng/L for ages ≥50 years, were shown to be highly sensitive and specific for the

Table. Summary of Indicators.

I	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
IIb	Usefulness/efficacy is less well established by evidence/opinion.
III	Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

Adapted from Christenson RH.³

diagnosis of acute HF.⁶ NT-proBNP values <300 ng/L had a negative predictive value of 99% for ruling out acute HF. Since both assays are expensive, they should only be used to improve the diagnostic accuracy for detecting HF when there are ambiguous signs and symptoms of HF.⁷

There is a lack of good evidence for the use of BNP or NT-proBNP for the diagnosis of HF in non-acute ambulatory patients. Unlike the acute setting, there is currently not enough information available on the cut-offs to use for decision-making in an outpatient setting. However, information published after the release of the Guidelines, indicates that when the levels are high enough, the risk for morbidity and mortality in HF appears to increase significantly, for example, when the NT-proBNP level is >1000 ng/L.⁸ More studies are required to correctly define appropriate cut-offs. The Guidelines do suggest that the current cut-offs defined for emergency department use are likely to be useful in excluding a diagnosis of HF.

II. Recommendations for Use of Biochemical Markers for Risk Stratification of HF

Class IIa: Level of Evidence: A

1. Blood BNP or NT-proBNP testing can provide a useful addition to clinical assessment in selected situations when additional risk stratification is required.

Class IIa: Level of Evidence: B

2. Serial blood BNP or NT-proBNP concentrations may be used to track changes in risk profiles and clinical status among patients with heart failure in selected situations where additional risk stratification is required.

Class IIb: Level of Evidence: B

1. Cardiac troponin testing can identify patients with heart failure at increased risk beyond the setting of acute coronary syndromes.

Class III: Level of Evidence: B

1. Routine blood biomarker testing for the sole purpose of risk stratification in patients with heart failure is not warranted.

Comment on the Use of Biochemical Markers for Risk Stratification of HF

There is general agreement from a number of studies that BNP and NT-proBNP can provide additional useful information for risk stratification in HF patients. A systematic review of the literature published in the British Medical Journal, that was not cited in the Guidelines, showed that BNP levels provide strong prognostic information, with every 100 ng/L increase associated with a 35% increase in the risk of death.⁹ Both BNP and NT-proBNP have strong prognostic value in patients with stable coronary artery disease and display nearly identical test performance in predicting all-cause mortality for HF.¹⁰ Persistent elevation of NT-proBNP three to six months after an acute coronary syndrome event is associated with chronically impaired LV function.¹¹

The Guidelines suggest that serial measurements of BNP and NT-proBNP levels can be used to track changes in risk and clinical status. However, a number of publications suggest that there is a significant biological variation for both assays. Wu provides a summary of studies of biological variation with mean values for healthy subjects and patients with stable HF for BNP ranging from 25% to 71% and NT-proBNP from 11% to 47%.¹² Several studies suggest that serial BNP levels need to change by a minimum of 70% to constitute a significant change over one week in stable HF patients, and NTproBNP levels need to change by at least 50%.^{13,14} The biological variability of these markers in acutely decompensated patients is not well understood because clinical improvement should be associated with a large change in natriuretic levels. However, the degree of intra-individual variability may be less important than in outpatients with stable HF. The guidelines suggest that for a difference in serial results for BNP or NT-proBNP levels to be significant, the levels should increase by approximately

85% or decrease by 46%. Therefore, changes in the serial levels of BNP and NT-proBNP need to be interpreted with care until a better understanding of how biological variation may affect serial results.

There are a number of reports in the literature that show that persistent elevations of cardiac troponin I or troponin T levels in the absence of detectable myocardial ischaemia are associated with poor long-term prognosis with or without HF.^{15,16} Troponin levels are strong independent predictors of mortality in patients with HF. These assays are relatively inexpensive, widely available and can be used to risk-stratify HF patients. In a study, not cited in the Guidelines, of patients with HF due to various aetiologies, both cTnT and BNP were independent prognostic factors, and patients with elevations of both cTnT and BNP had the poorest prognosis.¹⁷

III. Recommendations for Use of BNP and NT-proBNP in Screening of HF

Class IIb: Level of Evidence: B

1. Blood BNP or NT-proBNP testing can be helpful to identify selected patients with left ventricular systolic dysfunction in the post-infarction setting or to identify patients at high risk of developing heart failure (e.g. history of myocardial infarction, diabetes mellitus). However, the diagnostic ranges and cost-effectiveness in different populations remain controversial.

Class III: Level of Evidence: B

1. Routine blood natriuretic peptide (BNP or NT-proBNP) testing is not recommended for screening large asymptomatic patient populations for left ventricular dysfunction.

Comment on the Use of BNP and NT-proBNP in Screening of HF

Several studies cited in the guidelines have shown that the more elevated the BNP or NT-proBNP levels are, the greater the chance of identifying an individual with HF when screening a population who have stable coronary artery disease.^{18,19} However, there have been inconclusive results from a number of studies on the use of BNP or NT-proBNP for screening people with substantial left ventricular dysfunction known as asymptomatic left ventricular dysfunction (ASLVD) that do not have symptoms of HF.

The best potential application for these assays in patients with ASLVD may be to use their good negative predictive values to rule-out disease. One of the main stumbling blocks for the implementation of these assays as screening tests is the lack of randomised studies demonstrating that screening a population for ASLVD alters the natural history of the condition.

IV. Recommendations for Use of Biochemical Markers in Guiding Management of HF Patients

Class III: Level of Evidence: B

1. Routine blood BNP or NT-proBNP testing is not warranted for making specific therapeutic decisions for patients with acute or chronic heart failure because of the still-emerging but incomplete data as well as intra- and inter-individual variations.

Comment on the Use of Biochemical Markers in Guiding Management of HF Patients

Several studies have been published indicating a significant reduction in clinical events can be achieved using natriuretic peptide levels to guide therapy compared with standard clinical assessment.²⁰⁻²² However, there is no general consensus and the results of several larger randomised trials that are currently underway are required before any final conclusions can be made.

Analytical Issues for HF Biomarkers

The second of the two articles discusses the steps required for characterisation of new BNP or NT-proBNP assays prior to use as biomarkers for HF.² The article provides a comprehensive list of factors that need to be considered prior to the implementation of a new assay. Some of the more important points are listed below.

1. Validation Studies

All commercial assays for BNP and NT-proBNP should have analytical and clinical assay validation studies in peer-reviewed literature. Assays that do not provide adequate information should be used with caution.

2. Interferences in Assays of BNP and NT-proBNP

Immunoassays for both BNP and NT-proBNP use antibodies directed to different epitopes on the antigen molecules. A better understanding of possible cross-reactivity that may occur with the split products of NT-proBNP is required, along with ways to minimise potential interferences from heterophilic antibodies and rheumatoid factor for each assay.

3. Specimen Requirements

EDTA anticoagulated whole blood or plasma are the only specimens that can be used for the BNP assay. Samples should ideally be collected on ice and processed rapidly to avoid in vitro degradation. In reality, BNP is stable for four hours at room temperature or 24 h at 2-4 °C and NT-proBNP is stable for 72 hours at 2-4 °C. Serum or heparin plasma can be used for the NT-proBNP assay.²³

4. Other Factors that affect BNP and NT-proBNP Levels

a. Elevated levels of BNP and NT-proBNP are not

specific for HF and may be affected by a range of cardiac and non-cardiac conditions, including age, gender, ethnicity, myocardial ischaemia, cardiac arrhythmias, sepsis, shock, anaemia, renal failure, hypoxia, acute pulmonary embolism, pulmonary hypertension, and acute respiratory distress syndrome. Renal impairment has been shown to increase NT-proBNP levels and BNP levels to a lesser extent.

- b. There is an inverse relationship with body mass index (BMI) and the results for both assays are affected by obesity in patients either with or without chronic HF.
- c. The BNP assay will give falsely elevated results in patients treated for HF with the drug Nesiritide (Natracor, human recombinant BNP), since this drug is identical to endogenously released BNP. The NT-proBNP assay is not directly affected by this drug. However, Nesiritide is not licensed for sale in Australia but may be approved for use in selected situations.
- d. Both BNP and NT-proBNP have a high intra-individual biological variability.
- e. Both assay results should be reported in ng/L, rather than pmol/L since there are a number of forms of natriuretic peptide being measured in the assays.

Cost Effectiveness

The cost effectiveness of these assays was not covered in the Guidelines but is an important issue for the widespread implementation of these tests. Medicare Australia only provides a rebate for tests when requested for the diagnosis of HF in patients presenting with dyspnoea to a hospital emergency department. The rebate for BNP and NT-proBNP has been set at \$59.55 and is an expensive test compared to other clinical biochemistry assays. The cost-effectiveness of these assays was studied in the Acute Shortness of Breath Evaluation (BASEL) study.⁵ In this study the use of a point-of-care test for BNP significantly reduced the need for hospital admissions and the time to discharge was reduced from a median of 11 days in the control group to eight days in the BNP group. The cost of treatment in the BNP group was 26% lower than the control group. Therefore, the cost to the Health System may well be lower with the introduction of these assays.

Conclusions

The weight of evidence suggests that measuring BNP or NT-proBNP is of benefit to the patient when used in the correct clinical context. BNP or NT-proBNP levels must be used to complement clinical findings, not used as stand-alone tests, and any confounding factors that are known to affect results are taken into account e.g. obesity.

At present, the only area where BNP or NT-proBNP can be reliably used is in the acute setting to rule out or confirm HF,

in patients presenting with ambiguous signs and symptoms. There is currently inadequate evidence to recommend the use of these assays in patients with symptoms suspicious of HF in the non-acute setting and more information is required to determine appropriate cut-offs for this group of patients. It is anticipated that the assay results may provide some information on risk stratification of patients. As outlined in the NACB Guidelines, apart from these few circumstances, more robust evidence is required before BNP or NT-proBNP assays can be recommended for widespread use.

Competing Interests: None declared.

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