

B-Type Natriuretic Peptide (BNP) or N-Terminal-ProBNP (NT-proBNP)

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SYNOPSIS AND RELEVANCE

BNP is frequently used in the evaluation of dyspnea and to assess risk and prognosis of patients with congestive heart failure (CHF). Rational use of BNP or NT-proBNP can improve patient care by:

1. Helping to differentiate dyspnea in patients caused by pulmonary dysfunction from dyspnea caused by CHF.
2. Stratifying risk and prognosis in patients with CHF.
3. Avoiding confusion or misinterpretation of fluctuating BNP or NT-proBNP levels due to change in fluid status or biologic variation by decreasing unnecessary repeat testing before pharmacologic therapy of CHF can show effectiveness.

OBJECTIVES

1. Encourage use of BNP or NT-proBNP to help differentiate pulmonary causes of dyspnea from cardiac causes.
2. Encourage use of BNP or NT-proBNP to stratify cardiovascular morbidity and mortality in patients with CHF.
3. Understand the limited utility of serially measured BNP or NT-proBNP due to biologic variation and lack of target values.

BACKGROUND

B-type natriuretic peptide (BNP), formerly known as brain type natriuretic peptide is a member of a family of four natriuretic peptides. BNP is stored as a polypeptide precursor, proBNP, in secretory granules in both ventricles and, to a lesser extent, in the atria.¹ After proBNP is secreted in response to volume overload and resulting myocardial stretch, it is cleaved to a biologically inert N-terminal fragment NT-proBNP and a biologically active hormone, BNP.

BNP or NT-proBNP levels are useful in distinguishing heart failure (HF) from other causes of dyspnea. Diagnostic rules developed for HF have found that the BNP or NT-proBNP levels add greater diagnostic value to the history and physical examination than other initial tests (electrocardiogram, chest radiograph, and initial blood tests)^{2,3} Both BNP and NT-proBNP are produced in equal amounts, and while either fragment can be measured by immunoassays, the clinical cutoff values differ. Most dyspneic patients with HF have BNP values above 400 pg/mL, while BNP values below 100 pg/mL have a very high negative predictive value for HF as a cause of dyspnea.⁴ In the range between 100 and 400 pg/mL, plasma BNP

concentrations are not very sensitive or specific for detecting or excluding HF. Other diagnoses, such as pulmonary embolism, left ventricular (LV) dysfunction without exacerbation, LV hypertrophy, and cor pulmonale, should also be considered in patients with plasma BNP concentrations in this range. In normal subjects, the plasma concentrations of BNP and NT-proBNP are similar (approximately 10 pmol/L). However, in patients with LV dysfunction, plasma NT-proBNP concentrations are approximately fourfold higher than BNP concentrations.⁵

BNP assays vary between manufacturers while NT-proBNP assays are standardized, so there is no simple conversion factor to compare BNP and NT-proBNP levels. An NT-proBNP level greater than (>) 900 pg/mL provides roughly equivalent accuracy as a BNP level of >100 pg/mL for diagnosis of HF. The optimal values for distinguishing HF from other causes of dyspnea vary with patient age. In a large multicenter study, for patients less than (<) 50, 50 to 75, and >75 years of age, the optimal plasma NT-proBNP cutoffs for diagnosing HF were 450 pg/mL, 900 pg/mL, and 1800 pg/mL, respectively.⁶ Overall, these cutoffs yielded a sensitivity and specificity of 90 and 84 percent, respectively. Across the entire population, NT-proBNP levels below 300 pg/mL were optimal for excluding a diagnosis of HF, with a negative predictive value of 98 percent.

BNP results in natriuresis, diuresis, and reduction in blood pressure through vasodilation. This helps the heart pump more effectively. BNP is cleared from the circulation by natriuretic peptide receptors and plasma endopeptidases. Plasma BNP concentrations can vary with the assay used (due to different manufacturer antibodies), age, sex, and body mass index.⁷ The normal values tend to increase with age and to be higher in women than men. Plasma concentrations of NT-proBNP are also higher in older individuals and in women than men.⁸ On the other hand, both plasma BNP and NT-proBNP are lower in obese individuals,⁹ indicating that optimal reference intervals should account for age, gender, and body mass index (or other measure of body composition). In addition, NT-proBNP increases with renal failure to a greater extent than BNP, and optimal cut-off values for diagnosis in such patients have not been clearly established.¹⁰

Both BNP and NT-proBNP are used clinically and the test offered at a specific hospital depends on clinical preference and the available laboratory instrumentation as NT-proBNP is proprietary to one diagnostic manufacturer. Hospitals rarely need both BNP and NT-proBNP tests.

Elevated natriuretic peptide levels should be interpreted in the context of other clinical information; they may lend weight to the diagnosis of HF or trigger consideration of HF but should not be used in isolation to diagnose HF. Patients may present with more than one cause of dyspnea (such as pneumonia and an exacerbation of HF). Thus, a high plasma BNP or NT-proBNP concentration does not exclude the presence of other diseases. Elevated BNP/NT-proBNP levels may be seen in right ventricular dysfunction secondary to pulmonary hypertension or embolus, in atrial fibrillation as a small amount is produced in the atria, and in obese patients.

Along with reduced renal function, diabetes, low ejection fraction and age greater than 60, elevated levels of BNP have been associated with increased risk of mortality from CHF.¹¹ Guidelines from the American College of Cardiology and American Heart Association recommend use of plasma BNP/NT-proBNP measurements to assess risk and prognosis in patients with known HF.^{12,13} For example, measurement of BNP/NT-proBNP in heart failure patients at discharge provides prognostic information about risk of death and readmission within 6 months.^{14,15} In addition, BNP/NT-proBNP may be used to differentiate between cardiac and non-cardiac causes of dyspnea of uncertain etiology, and as a diagnostic adjunct when the clinical diagnosis of heart failure is uncertain, especially in the acute care setting.¹⁶

New dual drug therapies, sacubitril/valsartan (Entresto), that include an angiotensin receptor neprilysin inhibitor (ARNI) (sacubitril) combined with an angiotensin receptor blocker (valsartan) are aimed at reducing the risk of cardiovascular death and hospitalization for patients with CHF and reduced ejection fraction. Since BNP is degraded by neprilysin, treatment with ARNI causes elevation of BNP levels. NT-proBNP is not degraded by neprilysin, and its levels are not increased by neprilysin inhibition. Some have recommended use of NT-proBNP

because of the effect of neprilysin inhibition on BNP levels,¹⁷ while other studies have recommended monitoring both BNP and NT-proBNP.¹⁸ However, the clinical and analytical studies are limited, and the diversity of both BNP and NT-proBNP assays used in clinical laboratory practice have not been adequately evaluated to provide an evidence-based conclusion regarding the appropriate assay to use when a patient is treated with ARNI.¹⁹ BNP and NT-proBNP should never be ordered together during CHF treatment or with ARNI, and either BNP or NT-proBNP have shown comparable prognostic performance in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial.

The use of serial measurements of plasma BNP or NT-proBNP to manage patients with heart failure remains debatable and is not, as yet, validated or recommended for routine care. Excellent reviews and analysis of this controversial issue can be found in the references listed below.²⁰⁻²² A number of factors confound the use of plasma BNP or NT-proBNP for monitoring in heart failure, including wide biological variation, lack of appropriate target values, failure to show an impact on morbidity or mortality, and questionable impact on clinical management.

Nevertheless, if serial measurements are used for heart failure management, the minimum time interval needed to observe any correlation with outcome and plasma BNP or NT-proBNP values from therapy is at least 2 to 4 weeks in outpatients,²³ and several clinical trials have used serial measurements every 12 weeks. For inpatients, a commonly accepted interval for BNP or NT-proBNP testing is once per admission.^{24,25}

Population studies also show that an elevation in plasma BNP or NT-proBNP has predictive value for the development of HF or other cardiovascular events in patients with stable angina and acute coronary syndrome.¹² However, there are no guidelines or recommendations for routinely using BNP or NT-proBNP for this purpose. It has also been reported that measurement of BNP and NT-proBNP is of little value for predicting the prognosis of, or monitoring the clinical status of, critically ill patients.²⁶

This information may be used to guide utilization practices; specifically, to assess the indications for, and frequency of, plasma BNP or NT-proBNP testing. For example, frequent (eg, daily) monitoring of plasma BNP or NT-proBNP in inpatients would be difficult to justify as an appropriate clinical practice. In this case, an intervention may be warranted to control unnecessary testing. As one example, Lum²⁵ reported on the use of a protocol that required cardiologist approval for repeat BNP measurements that successfully reduced unnecessary testing. Others have seen benefit from the implementation of clinical decision support tools to reduce unnecessary BNP testing, as well as several other analytes.²⁴

The objective of this module is to evaluate the use of BNP or NT-proBNP in your practice setting. Suggested procedures are given for collecting and analyzing data regarding test-ordering practices. Based on the findings, several potential interventional strategies are provided for your consideration, if needed.

INSIGHTS

1. BNP or NT-proBNP is useful to predict morbidity and mortality in congestive heart failure (CHF).
2. BNP or NT-proBNP is useful to differentiate pulmonary causes of dyspnea from cardiac causes of dyspnea (CHF).
3. Repeat or serial BNP or NT-proBNP levels are of dubious value in inpatients.
4. Either BNP or NT-proBNP can be used to monitor patients treated with neprilysin inhibitors.
5. BNP or NT-proBNP is frequently overutilized and auditing test utilization may be a valuable intervention. Utilization.²⁵

INTERVENTIONS

1. Review or establish consensus guidelines for the appropriate use of BNP or NT-proBNP among medical staff in your practice setting based on when and how often to test. These criteria can be used to measure compliance with utilization of BNP or NT-proBNP. A common testing frequency for BNP or NT-proBNP in inpatients is once per admission. Some clinicians may feel a need to obtain a BNP or NT-proBNP just prior to discharge to establish a baseline. For outpatients, repeat BNP or NT-proBNP tests should not typically be

performed within 2 weeks following an intervention. Additional monitoring with BNP or NT-proBNP has no known additional benefit or correlation with prognosis. For this module, interventions and assessments are centered upon inpatients, as interventions in an outpatient setting are difficult to determine.

2. Collect data on BNP or NT-proBNP utilization patterns, if available from information systems. If access to data is limited, use laboratory test logs over several weeks to collect information about frequency of retesting; these data can be analyzed with a spreadsheet. Basic assessment should include BNP or NT-proBNP ordering practices by patient as percentage retested too frequently based on your criteria, eg, ≤ 2 per 7 days).
3. If repeat testing rates are high, perform additional analysis by location and/or provider to look for atypical utilization trends and provide feedback by clinician and/or patient location.
4. Review standing orders, panels, etc. that contain BNP or NT-proBNP to confirm that they are appropriately designed and used. Modify or eliminate as needed to improve utilization.
5. Consider using order systems to develop soft or hard stops if BNP or NT-proBNP is ordered too frequently. Possible interventions include:
 - a. Add comments to BNP or NT-proBNP order forms or order entry screens to inform clinicians about proper use of the test at the time of order, based on guidelines developed by the medical staff.
 - b. Use different names for the same test to guide appropriate utilization. For example, inpatient orders might be limited to BNP (admission) and BNP (discharge).
 - c. Create a “pop-up” or other alert (soft-stop) whenever BNP or NT-proBNP is reordered too soon. The clinician may override the alert.
 - d. Create a hold (hard-stop) on the order, if reordered too soon, with a requirement for additional action (eg, cardiology approval, additional justification) as appropriate for your clinical setting.
 - e. Automatically cancel repeat BNP or NT-proBNP orders (hard-stop) with instructions for how to override the order cancellation (eg, call laboratory).

INTERVENTION ANALYSIS

Assessing the utilization of BNP or NT-proBNP is straightforward for inpatients (see **Appendix A**).

1. Determine the number of BNP or NT-proBNP tests performed over a period of time (eg, 12 months).
2. Determine the number of duplicate BNP or NT-proBNP tests performed, as determined by your guidelines, over the same period of time.
3. Identify providers and/or patient locations with the most repeat BNP or NT-proBNP tests.
4. After interventions have been implemented, determine the number of BNP or NT-proBNP tests and the number of duplicate BNP or NT-proBNP tests performed over a suitable time interval (eg, 1 to 2 months).
5. Calculate % improvement in BNP or NT-proBNP test utilization and the number of BNP or NT-proBNP test reductions annually (see **Appendix B**).

APPENDIX A: BNP DUPLICATES VOLUME, PRE-INTERVENTION

Collect the data below for a defined period (1-12 months depending on ease of collection) for inpatients, using the same time period for pre- and post-intervention measurements. These data will serve as a baseline measure of BNP utilization. The results will be compared to data obtained after interventions have been made to reduce BNP use.

A1: # Total BNP or NT-proBNP tests	
A2: # BNP or NT-proBNP duplicates (per your guidelines)	
A3: Time period in months	

APPENDIX B: POST-INTERVENTION FOLLOW-UP DATA

B1: Total # of BNP or NT-proBNP tests performed post-intervention	
B2: # of BNP or NT-proBNP duplicates (per your guidelines), post-intervention	
B3: Post-intervention period in months	
B4: % Improvement in BNP or NT-proBNP utilization = $100 * (A2 - B2)/A2$	

QUESTIONS AND ANSWERS

QUESTION 1 OBJECTIVE

Become familiar with the clinical indications of BNP or NT-proBNP.

QUESTION 1

BNP or NT-proBNP is NOT useful in which of the following scenarios?

- A. Provide prognostic information regarding CHF.
- B. Differentiate between cardiac and non-cardiac causes of dyspnea.
- C. Provide prognostic information in patients with acute coronary syndrome.
- D. Serial measurement to titrate pharmacologic interventions for CHF.

The correct answer is D. Serial measurements of BNP or NT-proBNP have not been shown to conclusively help guide interventions in CHF due to the lack of an accepted target range, physiologic variation, and the natural delay in response to therapy.

A is incorrect. BNP or NT-proBNP is well recognized to stratify risk of mortality in CHF.

B is incorrect. BNP or NT-proBNP can help to differentiate dyspnea of pulmonary origin from cardiac origin.

C is incorrect. BNP or NT-proBNP provides morbidity and mortality information in patients with acute coronary syndrome.

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QUESTION 2 OBJECTIVE

Become familiar with the physiologic actions of BNP.

QUESTION 2

Which of the following statements regarding BNP is INCORRECT?

- A. BNP levels can be increased in cases of pulmonary embolus.
- B. BNP is primarily produced within cardiac atria.
- C. BNP results in natriuresis and diuresis.
- D. BNP is elevated in left ventricular dysfunction.
- E. BNP helps to reduce blood pressure.

The correct answer is B. BNP is primarily produced within cardiac ventricles.

A is incorrect. BNP is produced in response to ventricular filling pressures, which can be increased in the right ventricle secondary to pulmonary dysfunction.

C is incorrect. BNP results in natriuresis and diuresis and reduction in blood pressure by inhibiting the renin-angiotensin-aldosterone system.

D is incorrect. BNP is produced and released in response to increased left ventricular pressure caused by ventricular dysfunction.

E is incorrect. BNP reduces blood pressure by inhibiting the renin-angiotensin-aldosterone system.

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QUESTION 3 OBJECTIVE

Become familiar with the risk factors for congestive heart failure.

QUESTION 3

Which of the following is NOT an indicator of high risk in a patient with CHF?

- A. Renal insufficiency
- B. Diabetes
- C. Age greater than 60
- D. Elevated BNP or NT-proBNP
- E. Persistent New York Heart Association class I or II symptoms

The correct answer is E. Persistent New York Heart Association Class I or II symptoms. In class I, symptoms are absent, while in class II they are mild and typically consist of mild shortness of breath or angina when walking. Class III and IV symptoms are associated with high risk and consist of marked limitations in activity with comfort only at rest (class III) or symptoms while at rest (class IV).

A is incorrect. Cardiac and renal function are highly correlated; dysfunction in one causes dysfunction in the other. This is often known as the cardio-renal syndrome.

B is incorrect. Diabetes is one of the strongest predictors of poor outcome in CHF.

C is incorrect. Age greater than 60 is a strong predictor of poor outcome in CHF.

D is incorrect. Ejection fraction < 45% is associated with a poor outcome.

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QUESTION 4 OBJECTIVE

Become familiar with conditions that alter serum BNP Levels.

QUESTION 4

Which of the following does not affect plasma BNP levels?

- A. Renal insufficiency
- B. Obesity
- C. Liver dysfunction
- D. Pulmonary hypertension
- E. Atrial fibrillation

The correct answer is C. The liver has no role in the clearance of BNP or NT-proBNP. While NT-proBNP is more severely affected by renal insufficiency than BNP, both are increased in renal dysfunction. Obesity results in lower levels of BNP, and both atrial fibrillation and pulmonary hypertension can increase BNP levels.

A is incorrect. While NT-proBNP is more severely affected by renal insufficiency than BNP, both are increased in renal dysfunction.

B is incorrect. Obesity results in lower BNP levels

D is incorrect. Pulmonary hypertension, particularly when associated with right ventricular dysfunction, can lead to increases in BNP.

E is incorrect. Atrial fibrillation has been associated with increases in BNP.

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