



CIGNA MEDICAL COVERAGE POLICY

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Subject Plasma Brain Natriuretic Peptide

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Cardiac Disease Risk Assessment:
Emerging Laboratory Evaluations

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Coverage Policy

CIGNA covers the measurement of plasma brain natriuretic peptide (BNP) or NT-proBNP as an adjunct to other clinical testing as medically necessary for any of the following:

- differentiating heart failure from pulmonary disease in dyspneic individuals
- monitoring response to treatment for heart failure
- risk stratification of individuals with suspected acute coronary syndromes

General Background

The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines describes heart failure as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. Because not all patients have volume overload at the time of initial or subsequent evaluation, the term heart failure is preferred over the older term congestive heart failure (CHF) (Hunt, et al., 2005). Heart failure may affect the right side, the left side, or both sides of the heart. As the heart's pumping action is lost, blood may back up into other areas of the body, such as the liver, gastrointestinal tract, extremities and lungs. Many organs don't receive enough oxygen and nutrients, which damages them and reduces their ability to function properly. Most areas of the body can be affected when both sides of the heart fail. Symptoms of heart failure may include weight gain, swollen feet and ankles, shortness of breath, fatigue and loss of appetite. It is important to identify the underlying cause of heart failure in

order to provide specific treatment (National Institutes of Health [NIH], 2006). Causes of heart failure include cardiac and non-cardiac causes (e.g., hypertension, coronary heart disease, valvular heart disease, pericardial disease, thyroid disorders, and infiltrative diseases such as amyloidosis) (Institute for Clinical Systems Improvement [ICSI], 2007).

Heart failure is difficult to diagnose clinically in its early stages. Heart failure is traditionally diagnosed by a history and physical examination. Supplementary diagnostic testing includes chest radiography, echocardiography, right-sided heart catheterization, and the six-minute walk test. An inexpensive, simple, rapid and objective test that can be conducted at the point of care to aid diagnosis is valuable to the clinician, as there may be many reasons for a patient's sudden onset of shortness of breath. Therefore, natriuretic peptides have been researched for such a test due to their ability to aid in the diagnosis and management of heart failure. A prognosis in heart failure is generally made by calculating a patient's heart failure survival score (HFSS), which combines the results of commonly obtained, noninvasive, objective tests to stratify the patient's risk of future morbidity and mortality (ICSI, 2005; Cardarelli and Lumicao, 2003; Aaronson, et al., 1997).

Brain-type natriuretic peptide (BNP) was originally cloned from extracts of porcine brain, although the peptide is mainly synthesized, stored, and released from the myocardium of the ventricles. The substance starts as preproBNP, an amino acid peptide which is broken down into the peptide pro-BNP and a fragment. Pro-BNP is enzymatically cleaved into the biologically active BNP and the inactive N-terminal fragment known as NT-proBNP, both of which circulate in the plasma. BNP levels rise in response to an increase in ventricular wall stretch and end-diastolic volume. Since BNP has a half-life of 22 minutes, it may reflect acute changes in cardiac state to a greater extent than chronic cardiac states. BNP levels rise in response to the left ventricular wall stress associated with heart failure. NT-proBNP has a longer half life of 120 minutes, which has led to studies of NT-proBNP as an indicator of hemodynamic changes such as serial measurements every 12 hours. Due to a greater use of BNP reported in the literature, and the fact that NT-proBNP may not reflect the patient's status at the time of examination due to its longer half-life, BNP is typically considered the gold standard natriuretic peptide for clinical applications (ICSI, 2005).

Studies have evaluated the diagnostic, prognostic and therapeutic monitoring value of BNP and NT-proBNP testing in patients with heart failure. Plasma BNP and NT-proBNP concentrations correlate with elevated end-diastolic pressure, which closely parallels dyspnea in heart failure. This suggests that these biomarkers are uniquely suited to provide accurate neurohormonal profiling in heart failure, increasing as heart failure progresses. Normal BNP or NT-proBNP levels have a high negative predictive value for the exclusion of heart failure. Use of these tests to rule out heart failure may save the patient from additional invasive and uncomfortable testing for heart failure, such as echocardiogram and right heart catheterization, and allow care to focus on other reasons for shortness of breath. In patients with elevated BNP or NT-ProBNP levels, the degree of elevation correlates with the severity of heart failure, according to the New York Heart Association* classification system (see page 10). BNP is elevated in patients who have right heart failure, but the degree of elevation is not as great as BNP elevation from left ventricular dysfunction. BNP levels may also be affected by age, sex, weight, and renal function (ICSI, 2007; Christ, et al., 2006; Hunt, et al., 2005, Krauser, 2005; Winter and Elin, 2004).

Masson et al. (2006) performed a direct comparison of BNP and NT-proBNP in patients with chronic and stable heart failure. The authors reported that both natriuretic peptides showed subtle differences in their relation to clinical characteristics and prognostic performance. NT-proBNP performed slightly better than BNP for predicting outcome, in particular for death from pump failure and hospitalization for heart failure.

U.S. Food and Drug Administration (FDA)

On November 20, 2000, the FDA classified BNP in vitro diagnostic devices from Class III designation to Class II (FDA, 2000). The FDA identifies this generic type of device as a clinical chemistry device, product code NBC. The generic type of device, a B-Type Natriuretic Peptide device is used as an aid in the diagnosis of patients with CHF. The 2000 Final Guidance for Industry and FDA Reviewers Class II Special Control Guidance Document for B-Type Natriuretic Peptide Premarket Notifications identifies "risks to health" which states, "the FDA has identified two risks to health associated with this type of device, a falsely low BNP and a falsely elevated BNP. A falsely low BNP could potentially delay diagnosis and treatment of congestive heart failure (CHF), but this risk is generally most applicable to asymptomatic patients. These patients would eventually become symptomatic due to progression of their disease, at which point further testing and treatment would be initiated. A falsely elevated BNP could result in unnecessary additional testing, e.g. a non-invasive

echocardiogram, in a patient without CHF. This possibility can be decreased by ruling out conditions known to be associated with an increased BNP level. The risks to health are minimized by premarket evaluation of a statistically valid, age-matched control clinical study of the population targeted in the intended use and by labeling describing the sensitivity, specificity, the area under the receiver operator characteristics (ROC) curve, and confidence intervals obtained when data from these studies are analyzed.” The FDA believes the following controls, when combined with the general controls of the Food Drug and Cosmetic Act, will provide reasonable assurance of the safety and effectiveness of this type of device: labeling, design controls, and clinical information (FDA, 2000).

A number of devices have received FDA 510(k) approval for evaluating circulating BNP and NT-proBNP levels. These devices can be found on the FDA Center for Devices and Radiological Health 510(k) database. An example of an FDA-approved BNP device is the Triage[®] B-Type Natriuretic Peptide (BNP) Test (Biosite, Inc., San Diego, CA). The test is intended to be used as an aid in the following (FDA, 2005):

- diagnosis of heart failure
- assessment of heart failure severity
- risk stratification of patients with acute coronary syndromes (ACS)
- risk stratification of patients with heart failure

The clinical supportive data in the 510(k) substantial equivalence determination decision summary device only template states the sponsor provided five peer-reviewed articles assessing the clinical utility of BNP measurements as an aid in the risk stratification of patients with heart failure. The references are not listed for the five articles but can be found in the sponsor labeling. The decision summary states that a systematic review by Doust et al. (2005) included the five articles previously mentioned which concluded that BNP was a strong prognostic indicator for patients with heart failure (FDA, 2005).

An example of a NT-proBNP test system is the Elecsys[®] proBNP Immunoassay (Roche Diagnostics Corporation, Indianapolis, IN). The intended use is as an aid in the diagnosis of individuals suspected of having CHF. The test is further indicated for the risk stratification of patients with ACS and CHF. Three peer-reviewed studies are listed as clinical supportive data in the 510(k) substantial equivalence determination decision summary device only template including James et al. (2003), Jernberg et al. (2002), and Fisher et al. (2003) (FDA, 2003).

Literature Review

Diagnosis of Heart Failure: The use of BNP as an aid in diagnosing heart failure in patients presenting to an acute care setting with dyspnea has been studied in several large trials. At a cutoff from 80–100 picograms/milliliter (pg/mL), BNP has a sensitivity of approximately 90%, specificity of approximately 73%, and diagnostic accuracy of approximately 81–83% (Maisel, et al., 2002; Morrison, et al., 2002; McCullough, et al., 2002; Dao, et al., 2001).

NT-proBNP has also been evaluated as a marker in the diagnosis of heart failure. The ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study evaluated the utility of NT-proBNP as a biomarker for heart failure and the optimal cutoff concentration for this use. In this controlled clinical trial, blinded study physicians clinically diagnosed 600 patients presenting to the emergency department with dyspnea. The clinical diagnosis was compared to results of NT-proBNP testing. Overall, at a concentration cutoff of 900 pg/mL, the test had a 90% sensitivity, 85% specificity, and diagnostic accuracy of 87%. At a cutoff concentration of 300 pg/mL, NT-proBNP had a negative predictive value of 99%. Age was determined to affect the sensitivity and specificity of the test in this population, with an optimal cutoff point of 450 pg/mL in patients under age 50 and 900 pg/mL in patients over age 50 (Januzzi, et al., 2005). Similar results were found in a study by Moe et al. (2007).

The data from the PRIDE study was pooled with that of two international studies and a prospective registry to comprise a cohort of 1256 patients in the International Collaborative of NT-proBNP (ICON) study (Januzzi, et al., 2006). The data were analyzed to determine the optimal N-proBNP concentrations indicative of heart failure in acutely dyspneic patients. The sensitivity and specificity of the test were influenced by patient age, with increased accuracy in identifying patients with heart failure when the cutoff concentration of NT-proBNP was 450 pg/mL, 900 pg/mL, and 1800 pg/mL for patients in age ranges < 50, 50–75, and > 75 years, respectively.

This stratification resulted in an overall sensitivity of 92%, specificity of 84%, positive predictive value of 86%, and diagnostic accuracy of 93%. Independent of age, the cutoff concentration of 300 pg/mL had a negative predictive value of 98%. In a multivariate analysis, NT-proBNP was the strongest independent predictor of heart failure.

A study by Baggish et al. (2006) supports the notion that NT-proBNP testing in combination with other signs and symptoms of heart failure is discriminative in diagnosing heart failure. A cohort of 599 patients was evaluated for factors, including interstitial edema on chest radiograph, orthopnea, absence of fever, age, and rales. The factors were weighted, and the combined score was found to improve diagnostic accuracy over NT-proBNP testing alone in patients suspected of acute heart failure.

In a cohort study, Mueller et al. (2005) sought to compare head-to-head the diagnostic accuracy of BNP and NT-proBNP for heart failure in a cohort of 251 patients who presented to the emergency room with a chief complaint of dyspnea. Cutoff concentrations of 295 ng/L for BNP and 825 ng/L for NT-proBNP were found to have the highest diagnostic accuracy (83% versus 84%, respectively), with sensitivity 80% versus 87%, respectively, and specificity 86% versus 81%, respectively. The authors also found that age, sex and renal function had no effect on the diagnostic utility of either test. The similar performance by these two tests suggests their equivalence in diagnosing heart failure in patients with dyspnea presenting to the emergency room.

O'Donoghue et al. (2005) sought to determine the effect of left ventricular ejection fraction (LVEF) on NT-proBNP and BNP levels in 153 patients with acute heart failure with a retrospective evaluation of the clinical data. Median NT-proBNP and BNP levels were significantly higher among patients with LVEF < 50% compared to those with LVEF ≥ 50%. BNP testing had a significantly higher false-negative rate than NT-proBNP testing in patients with LVEF ≥ 50% (20% versus 9%). This small, retrospective study suggests that there may be superiority in NT-proBNP testing over BNP testing in patients with preserved LVEF, but this needs to be confirmed with larger prospective studies prior to application in the broader population of patients with heart failure.

Another study supports the similarity of the utility of BNP and NT-proBNP testing in patients with suspected heart failure. Lainchbury et al. (2003) also conducted a head-to-head comparison of the utility of point of care and locally developed assays for BNP and NT-proBNP measurements in the diagnosis of heart failure in patients with acute dyspnea. Results of all assays were closely correlated. Optimum cutoff values varied somewhat by test. At the optimum cutoff levels, specificity was 70–89%, and sensitivity ranged from 80–94%.

In a randomized, controlled trial, Wright et al. (2003) reported the ability of the plasma measurement of NT-proBNP to improve the diagnostic accuracy of heart failure in primary care. Three hundred-five patients presenting to their general practitioner (GP) with symptoms of dyspnea and/or peripheral edema were randomly assigned to the experimental and control groups. GPs in the experimental group received the results of plasma NT-proBNP measurements to assist with their diagnostic process, while the GPs in the control group did not. The primary end point was the accuracy of the GP's diagnosis compared with that of a panel using the criteria from the European Society of Cardiology Guidelines for the diagnosis of heart failure. The experimental and control groups were comparable at baseline, except that the mean age of the control group was three years older than that of the experimental group. In these 305 patients, 77 met the panel's criteria for heart failure. The sensitivity and specificity were maximized at a cutoff of 100 pico-moles per liter (pmol/l). NT-proBNP measurement > 150 pmol/l improved the diagnostic accuracy from 49–70%, compared to the improvement from 52–59% without the NT-proBNP measurement. The main impact of the NT-proBNP assay was that it allowed GPs to rule out heart failure.

The 2005 ICSI Technology Assessment of BNP for the Diagnosis and Management of Heart Failure states that BNP testing is useful as an adjunct to other clinical tools for differentiating heart failure causes from other causes of dyspnea presenting in the urgent care center or emergency department. The diagnosis of heart failure is unlikely in patients with normal BNP levels. The authors reported that care needs to be taken when measuring BNP within 2–4 hours after the onset of acute symptoms, as false- negatives may occur. The utility of BNP needs to be defined as a tool to optimize management and treatment of heart failure. Furthermore, serial testing of BNP levels has not been shown to have clinical utility.

In a review by Mueller et al. (2007), the authors summarized that “BNP and NT-proBNP as single tests outperform all other variables available in the emergency department. Moreover, when used in conjunction with other clinical information, BNP and NT-proBNP significantly increase diagnostic accuracy.” The authors noted

that one of the drawbacks is when heart failure patients present with low BNP or NT-proBNP. The cause of heart failure may be secondary to causes upstream from the left ventricle, including mitral stenosis and acute mitral regurgitation.

Prognosis in Heart Failure: Many patients who have been hospitalized with acute exacerbations of heart failure have multiple rehospitalizations. The use of BNP and NT-proBNP testing may be a prognostic marker for morbidity and mortality in these patients.

As a secondary study objective, the ICON study (Januzzi, et al., 2006) sought to evaluate the utility of NT-proBNP as a short-term prognostic indicator in patients with heart failure. NT-proBNP levels were significantly higher in patients who died within 60 days of diagnosis than in those who survived. The optimal cutoff level for predicting mortality within 60 days was 5180 pg/mL, which had a sensitivity of 82%, specificity of 52%, positive predictive value of 19% and negative predictive value of 95%. Multivariable analysis determined NT-proBNP levels above 5180 pg/mL to be the strongest independent predictor of 60-day mortality in patients with heart failure.

In a prospective study by Harrison et al. (2002), using a cohort of 325 patients who had presented to the emergency room for heart failure, an initial BNP concentration of 480 pg/mL had a sensitivity of 68%, specificity of 88%, and accuracy of 85% in predicting death, hospital admission, or repeat emergency room visit within a six-month period after discharge. The authors found that higher BNP levels were associated with a worse prognosis.

Koglin et al. (2001) compared BNP levels with HFSS in a cohort of 78 patients. BNP levels were significantly associated with a change in cardiovascular functional class with time and correlated with HFSS. The authors reported that BNP levels have equivalent prognostic value with the HFSS and may reduce the need for the repetition of multiple tests to revise a prognosis in patients with heart failure.

Doust et al. (2005) conducted a systematic review of the literature detailing the potential for BNP to be used as a predictor of cardiac events and death in patients with heart failure. A total of 19 studies that used BNP values to estimate the relative risk of death or other cardiovascular events in heart failure patients and five studies that predicted risk in asymptomatic patients were included in the analysis. In heart failure patients, each increment of 100 pg/ml in BNP values was associated with a 35% increase in the relative risk of death. In 35 multivariate analysis models, BNP or NT-proBNP was the only variable to reach significance as a predictor in nine of them, meaning that other variables did not contain further prognostic information beyond the information provided by BNP/NT-proBNP. The authors reported that, although systematic reviews of prognostic studies have difficulties such as publication bias (i.e., lack of publication of negative results), BNP is a strong predictor of adverse outcomes in both asymptomatic and heart failure patients.

These studies support the utility of BNP and NT-proBNP testing at the time of symptom presentation as a prognostic indicator for patients with heart failure.

Monitoring Treatment for Heart Failure: In a multicenter randomized study, Jourdain et al. (2007) evaluated the benefit of BNP-guided therapy on outcomes in heart failure patients in clinical practice. The inclusion criteria were as follows: patients older than 18 years with symptomatic (New York Heart Association [NYHA] functional Class II to III) systolic heart failure defined by LVEF < 45% assessed by echocardiography using the American Society of Echocardiography guidelines, in stable condition (i.e., no hospital stay in the previous month), and treated by optimal medical therapy according to the European guidelines at the time of the study; dosages of medications were to be stable for at least one month before inclusion. Patients had to receive diuretics, angiotensin-converting enzyme inhibitor (ACEIs), or angiotensin II-receptor blockers (ARB) at the maximal tolerated dosage unless documented intolerance and beta-blockers approved for CHF, at the maximal tolerated dosage unless documented intolerance or specific contraindication. The exclusion criteria were as follows: ACS within three months, chronic renal failure (plasma creatinemia > 250 μ mol/l), documented hepatic cirrhosis, asthma, or chronic obstructive pulmonary disease. Patients were randomized into two groups:

- BNP group-medical therapy was increased with the aim of lowering plasma BNP levels (target < 100 pg/ml); each class of therapy could be modified according to the judgment of the investigator.

- Clinical group-medical therapy was adjusted according to the opinion of the investigator, on the basis of the physical examination and usual paraclinical and biological parameters.

The investigators were not allowed to measure plasma BNP level. Each group included 110 patients. The primary end point was emergency transplantation, death or hospitalization related to heart failure. The mean age of the participants was 65 years of age. Seventy-three percent were males. Patients had severe heart failure with a mean LVEF of $30 \pm 8\%$ and a mean left ventricular end-diastolic diameter of 67 ± 12 mm. The LVEF was slightly lower in the BNP group than the clinical group. The patients received maximal pharmacological therapy prior to entry in the study. Outpatient visits were scheduled each month for three months (titration phase), then every three months.

The investigators reported that at the end of three months, all types of drugs were changed more frequently in the BNP group. The mean dosages of ACEIs and beta-blockers was significantly higher in the BNP group ($p < 0.05$), whereas the mean increase in furosemide dosage was similar in both groups. During follow-up (median 15 months), significantly fewer patients reached the combined end point in the BNP group (24% versus 52%, $p < 0.001$). Event-free survival was better in the BNP group (84% versus 73% in the clinical group; $p < 0.001$). Two patients in the BNP group and ten patients in the clinical group were hospitalized twice or more for acute heart failure decompensation ($p < 0.05$). In the BNP group, the treatment was adjusted according to the plasma BNP level in 79% of the cases (106 of 134 treatment changes). The BNP target of < 100 pg/ml was reached in 16% of patients at baseline to 33% at three month follow-up ($p = 0.04$).

The reported limitations of this study are the patient population, which was young, mostly male, and limited to systolic dysfunction (LVEF $< 45\%$). The authors reported that most medical registers indicate that CHF patients are older and frequently female with prevalent diastolic dysfunction. The authors stated that "whether knowledge of BNP plasma level is beneficial through better evaluation of the CHF status of the patient or acts as a supplementary stimulus for increasing all drugs remains to be determined." (Jourdain, et al., 2007)

In a randomized, controlled clinical trial of 69 patients with heart failure, Troughton et al. (2000) compared BNP-guided treatment of heart failure to clinically-guided treatment and found reduced total cardiovascular events and delayed time to first event (e.g., death, hospital admission, or heart failure decompensation) in patients who were monitored with BNP levels. During the median ten-month follow-up, there were fewer total cardiovascular events in the BNP group than in the clinical group (19 versus 54, respectively, $p = 0.02$). At six months of follow-up, 27% of patients in the BNP group experienced a first cardiovascular event, compared to 53% in the clinical group. This study suggests promise in the use of BNP in clinical monitoring of patients with heart failure, but the small patient population reduces the power of the study and limits the applicability of the findings in clinical practice.

In another randomized, controlled trial, Murdoch et al. (1999) compared the efficacy of ACEI therapy titrated according to BNP levels with empiric ACEI therapy over eight weeks. The study included 20 patients with stable, mild to moderate heart failure undergoing conventional medical therapy, including ACEIs. The patients were randomized to two groups, 10 patients in the BNP group and 10 patients in the clinical group. In the BNP group, dosages of ACEIs were titrated based on serial BNP measurements toward the prospectively set target level of less than 50 pg/ml, although the rationale for this target BNP level was not specified. If the BNP concentration remained higher than 50 pg/ml despite a maximal dosage of ACEI, the AT1 receptor antagonist losartan was added at a dose of 25–50 mg once daily. In the clinical group, the dosage of ACEIs was increased according to the dosages shown to be of benefit in clinical trials, even when patients' symptoms were well-controlled. If patients remained symptomatic despite achieving this dose, the dosage could be increased further or losartan was added. There were no significant differences between the two groups in the severity of heart failure, LVEF, prescribed ACEIs, concomitant treatments, hemodynamic or neurohormonal parameters, and mean plasma BNP concentration at baseline. Only the BNP group was found to have a significant reduction in BNP levels during the treatment, a fall of 42% at four weeks, compared to 12% in the clinical group, but the difference diminished at eight weeks. In both groups, the treatment was hemodynamically well-tolerated. There was greater inhibition of the renin-angiotensin-aldosterone system and a larger fall in heart rate in patients whose medication was titrated according to BNP levels.

Evidence to support the utility of BNP and NT-proBNP testing in the management of patients with heart failure is limited but promising. Measurement of BNP levels as an adjunct to standard testing for monitoring the

effectiveness of therapy for patients with heart failure has become the standard of care in many heart failure clinics.

Prognosis in Other Cardiac Conditions/Acute Coronary Syndromes (ACS): Patients with ACS include those whose clinical presentations cover the following range of diagnoses: unstable angina, non–ST-elevation myocardial infarction, and ST-elevation myocardial infarction. The medical history, physical examination, electrocardiogram, assessment of renal function, and cardiac biomarker measurements in patients with symptoms suggestive of ACS at the time of the initial presentation can be integrated into an estimation of the risk of death and nonfatal cardiac ischemic events (Anderson, et al., 2007). Natriuretic peptides, which have been mainly used in the diagnosis of heart failure, have also been found to be elevated in patients with ACS. It has been reported that elevated BNP and NT-proBNP levels at admission in patients with ACS are associated with poor prognosis, including increased mortality, development of heart failure, and recurrent ischemic events (Kwan, et al., 2007).

In a prospective cohort study, Omland et al. (2007) assessed the association between BNP and NT-proBNP and the incidence of specific cardiovascular events in low-risk patients with stable coronary disease, the incremental prognostic information obtained from these two biomarkers compared with traditional risk factors, and their ability to identify patients who may benefit from ACE inhibition. Baseline plasma BNP and NT-proBNP concentrations were measured in 3761 patients with stable coronary artery disease and preserved left ventricular function participating in the PEACE (Prevention of Events With Angiotensin-Converting Enzyme Inhibition) study, a placebo-controlled trial of trandolapril. Multivariable Cox regression was used to assess the association between natriuretic peptide concentrations and the incidence of cardiovascular mortality, fatal or nonfatal myocardial infarction, heart failure, and stroke. The authors reported that the BNP and NT-proBNP levels were strongly related to the incidence of cardiovascular mortality, heart failure, and stroke but not to myocardial infarction. In multivariable models, BNP remained associated with increased risk of heart failure, whereas NT-proBNP remained associated with increased risk of cardiovascular mortality, heart failure, and stroke. By C-statistic calculations, BNP and NT-proBNP significantly improved the predictive accuracy of the best available model for incident heart failure, and NT-proBNP also improved the model for cardiovascular death. The magnitude of effect of ACE inhibition on the likelihood of experiencing cardiovascular end points was similar, regardless of either BNP or NT-proBNP baseline concentrations. The authors reported that in low-risk patients with stable coronary artery disease and preserved ventricular function, BNP provides strong and incremental prognostic information to traditional risk factors but does not provide a mandate for the use of peptides for tailoring therapy in individual patients. The authors stated that the clinical implications of an elevated BNP are unclear. The authors stated that the lack of prediction of myocardial infarction suggests that determination of BNP may not be useful for selection of anti-ischemic therapies in low-risk patients.

Richards et al. (2003) reported results of outcomes for a cohort of 666 patients who experienced an acute myocardial infarction and then followed up for three years to determine the prognostic value of BNP and NT-proBNP testing. BNP and NT-proBNP levels as well as LVEF were found to be predictive of future cardiovascular events, independent of other risk factors, and the combination of BNP or NT-proBNP testing with LVEF substantially improved risk stratification beyond that provided by either alone.

Jernberg et al. (2003) conducted a study to evaluate the utility of NT-proBNP levels for risk assessment and clinical decision-making in 2019 patients with unstable coronary artery disease. Elevated NT-proBNP was independently associated with mortality. Those with the highest levels of NT-proBNP (i.e., men with NT-proBNP levels above 906 ng/L and women with NT-proBNP levels above 1345 ng/L) who received conservative therapy had a fourfold increase in mortality over those whose levels were less. In those who were treated with invasive therapy, high NT-proBNP levels conferred a 3.5-fold increase in mortality. Those with a high BNP who were treated with an early invasive strategy had a reduced mortality of 7.3% compared to those who were treated conservatively.

A study by James et al. (2003) evaluated the utility of NT-proBNP as a prognostic indicator of subsequent mortality or myocardial infarction in a cohort of 6809 patients with non–ST-segment elevation ACS. Increased levels of NT-proBNP were associated with increased likelihood of short- and long-term mortality with those who had levels of 1869 pg/mL or higher having a one-year mortality rate of 19.2%. Among other risk factors, increased NT-proBNP was the most strongly associated with one-year mortality, but the combination of NT-proBNP with other risk factors provided the best risk stratification for mortality in patients with ACS.

Morrow et al. (2003) evaluated the utility of BNP levels for risk assessment and clinical decision-making in 1676 patients with ACS. At presentation, patients were randomized to receive either early invasive therapy with coronary angiography and revascularization, if feasible, or conservative therapy. Patients with baseline levels of BNP greater than 80 pg/mL were at significantly higher risk of death by 30 days after presentation (5.0% versus 1.2%). The association between elevated levels of BNP and mortality at six months was independent of other important clinical predictors available at presentation, including age, gender, diabetes, ST-segment depression, history of heart failure, heart failure at presentation and baseline cardiac troponin levels. Patients with elevated BNP at presentation had a significantly higher risk of developing new or worsening heart failure at 30 days (5.9% versus 1%) and at six months (9.1% versus 1.8%), independent of other clinical predictors. Patients who had invasive therapy had better outcomes overall. When the results were stratified by BNP level, there was no difference between invasive therapy versus conservative management in patients with higher levels of BNP. The authors reported that elevated BNP at presentation identified patients with non-ST-elevation ACS who are at higher risk of death and heart failure, and “further investigation is needed to identify therapies that may favorably modify the risk associated with increased levels of BNP in ACS” (Morrow, et al., 2003).

De Lemos et al. (2001) evaluated the use of BNP as a prognostic indicator in patients with ACS. This large study (n=2525) found an association between BNP levels and risk of death, heart failure, and myocardial infarction at 30 days and 10 months after the initial symptoms. Independent of other risk factors, a BNP level greater than 80 pg/mL was associated with an increased 10-month mortality rate in patients with ACS.

Body et al. (2006) reviewed the use of BNP as a potential marker of ACS. The authors found eight citations that addressed their study question, “In patients with suspected cardiac chest pain does measurement of BNP enable exclusion of ACS?” The authors reported that “BNP has shown promise as an early cardiac marker and may add prognostic stratification, although negative predictive value and positive predictive value may be unacceptably low to enable use as a sole cardiac marker. Incorporation into multimarker strategy is likely to be necessary. Serial estimations may enhance clinical utility” (Body, et al., 2006).

Recent textbook literature states, “A single measurement of BNP obtained in the first few days after the onset of ischemic symptoms, provides predictive information for risk stratification in ACS. NT-proBNP is also a marker of long-term mortality in patients with stable coronary disease and provides prognostic information above and beyond that provided by conventional cardiovascular risk factors and the degree of left ventricular systolic dysfunction. NT-proBNP is a stronger predictor of first cardiovascular events than cardio-CRP in subjects without known cardiovascular disease” (Ferri, 2007).

These studies support the utility of BNP and NT-proBNP testing at the time of symptom presentation as a prognostic indicator for patients with an ACS. Additional studies are needed to identify therapies that may modify the risk associated with increased levels of BNP and NT-proBNP testing in ACS.

Other Indications: There is some evidence to suggest that BNP levels may someday be useful in evaluating surgical indications in pediatric patients with ventricular septal defect (Kunii, et al., 2003). BNP levels may provide valuable information for the detection of infants with significant patent ductus arteriosus who require treatment (Choi, et al., 2005). BNP may provide future usefulness as a screening tool for left-ventricular dysfunction (McDonagh, et al., 1998, 2001; Maisel, et al., 2001; Vasan, et al., 2002; Hedberg, et al., 2004) or as a prognostic tool before the onset of clinically apparent cardiovascular disease (Wang, et al., 2004). BNP has been studied as a tool to assess outcomes in patients without heart failure who undergo atrial fibrillation ablation (Kurosaki, et al., 2007). Proposed uses of NT-proBNP include cardiac disease and dysfunction detection in the asymptomatic patient (Galvani, et al., 2004; Hartmann, et al., 2004; Pfister, et al., 2004; Bay, et al., 2003; Kragelund, et al., 2005) and risk stratification in hypertension (Hildebrandt, et al., 2004; Olsen, et al., 2004). BNP is being investigated as a biomarker for the diagnosis and risk stratification of patients with septic shock (Kandil, et al., 2008). Currently, there is limited data to support these indications. Additional research is needed to define the role of BNP and NT-proBNP in these clinical situations.

Professional Societies/Organizations

In 2007, the ACC/AHA published an update to their 2002 guidelines for the management of patients with unstable angina/non-ST elevation myocardial infarction. In the recommendations for early risk stratification, the authors added B-type natriuretic peptides as a newer biomarker. The recommendation states that measurement of BNP or NT-proBNP may be considered to supplement assessment of global risk in patients with suspected ACS. The guidelines state that numerous prospective studies and data from large data sets have documented

B-type natriuretic peptides' powerful prognostic value independent of conventional risk factors for mortality in patients with stable and unstable coronary artery disease. The guideline states that "studies in ACS showed that when measured at first patient contact or during the hospital stay, the natriuretic peptides are strong predictors of both short- and long-term mortality in patients with ST elevation myocardial infarction or unstable angina/non-ST elevation myocardial infarction" (Anderson, et al., 2007).

The 2006 Heart Failure Society Practice Guideline on Heart Failure states that determination of BNP or NT-proBNP concentration is not recommended as a routine part of evaluation of structural heart disease in patients at risk but without signs and symptoms of heart failure. It is recommended that BNP or NT-proBNP levels be assessed in all patients suspected of heart failure when the diagnosis is uncertain.

In the updated ACC/AHA practice guideline on heart failure (Hunt, et al., 2005), the guideline states that measurement of BNP (i.e., using assays for BNP or NT-proBNP, which yield clinically similar information) can be useful in the evaluation of patients presenting in the urgent care setting in whom the clinical diagnosis of heart failure is uncertain. BNP levels should not be used alone to confirm or exclude the presence of heart failure. In general, plasma BNP levels correlate positively with the degree of left ventricular dysfunction, but they are sensitive to other biological factors such as age, sex, weight, and renal function. It may also be useful in managing patients with heart failure, but more research will be necessary to determine its role in disease management. The guideline states that "many patients taking optimal doses of medications continue to show markedly elevated levels of BNP, and some patients demonstrate BNP levels within the normal range despite advanced heart failure. The use of BNP measurements to guide the titration of drug doses has not been shown to improve outcomes more effectively than achievement of the target doses of drugs shown in clinical trials to prolong life."

In 2005, the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology published updated guidelines for the diagnosis and treatment of chronic heart failure stating that BNP and NT-proBNP are used in clinical practice as 'rule out' tests to exclude significant cardiac disease. A low-normal concentration in an untreated patient makes heart failure unlikely as the cause of symptoms. Although BNP and NT-proBNP have high prognostic potential, their role in treatment monitoring remains to be determined (Swedberg, et al., 2005).

Summary

The evaluation of BNP may have utility in the urgent care setting, where it has been useful to differentiate dyspnea due to heart failure from pulmonary disease with acceptable sensitivity and specificity. Measurement of BNP levels as an adjunct to standard testing for monitoring the effectiveness of therapy for patients with heart failure has become the standard of care in many heart failure clinics. The measurement of BNP or NT-proBNP may be considered to supplement assessment of global risk in patients with suspected ACS. There is some evidence to suggest that BNP levels may be useful for additional clinical indications (e.g., screening tool for left-ventricular dysfunction, detection of infants with significant patent ductus arteriosus who require treatment). At the present time, the evidence for these indications is not well-supported. Additional research is needed to define the role of BNP and NT-proBNP in these clinical situations.

*New York Heart Association Functional Classification of Patients with Heart Disease

Classification	Characteristics
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, and dyspnea.
Class IV	Inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®*	Description
83880	Natriuretic peptide

ICD-9-CM Diagnosis Codes	Description
411.1	Intermediate coronary syndrome
411.81-411.89	Other acute and subacute forms of ischemic heart disease
428.0-428.43	Congestive heart failure
786.00-786.09	Dyspnea and respiratory abnormalities

*Current Procedural Terminology (CPT®) © 2007 American Medical Association: Chicago, IL.

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Policy History

<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	11/15/2007	0028	Plasma Brain Natriuretic Peptide

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