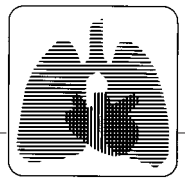


# reviews

# Brain Natriuretic Peptide in the Management of Heart Failure*

## The Versatile Neurohormone

*Simon de Denus, MSc(Pharm);† Chantal Pharand, PharmD; and David R. Williamson, MSc(Pharm)*

**Brain natriuretic peptide (BNP), also called B-type natriuretic peptide, is a member of a family of structurally related hormones, the natriuretic peptides. Current data suggest that measurement of BNP plasma concentrations is a useful tool in the diagnosis of acute heart failure in patients presenting to an emergency department with acute dyspnea. Furthermore, BNP constitutes a promising new marker of prognosis after an acute coronary syndrome episode and in patients with chronic heart failure. Nesiritide, the human recombinant form of BNP, is a new vasodilator used in the treatment of acute heart failure that has several potential advantages over current drug therapy.** ***(CHEST 2004; 125:652–668)***

**Key words:** brain natriuretic peptide; congestive heart failure; nesiritide

**Abbreviations:** ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ANP = atrial natriuretic peptide; AUC = area under the curve; BNP = brain natriuretic peptide; CHF = chronic heart failure; CI = confidence interval; CNP = C-type natriuretic peptide; NPR = natriuretic peptide receptor; NT = N-terminal; TIMI = Thrombolysis in Myocardial Infarction; VMAC = Vasodilation in the Management of Acute Congestive Heart Failure

Brain natriuretic peptide (BNP), also called B-type natriuretic peptide, is a member of a family of structurally related hormones, the natriuretic peptides. This family also includes atrial natriuretic peptide (ANP) and C-type natriuretic peptide (CNP). It has recently gained a lot of popularity as a potential marker for congestive heart failure. In addition, clinical studies using recombinant BNP (nesiritide) as a treatment strategy in the management of heart failure have been published. Hence, the purpose of this article is to review the usefulness of BNP as a biological marker and the usefulness of its applications in the management of congestive heart failure.

Articles were selected from those listed on MEDLINE from 1966 to February 2003 using the terms *brain natriuretic peptide*, *B-type natriuretic peptide*, and *nesiritide*. The bibliographies of all articles retrieved during the literature search subsequently were studied for articles that may have been missed during the computerized literature search.

*From the Philadelphia College of Pharmacy (Mr. de Denus), University of Sciences of Philadelphia, Philadelphia, PA; and Faculty of Pharmacy (Dr. Pharand and Mr. Williamson), Université de Montréal and Hôpital du Sacré-Coeur de Montréal, Montréal, QC, Canada.

†As part of his fellowship training, Mr. de Denus has served as a coinvestigator in Acute Decompensated Heart Failure Registry (ADHERE), which was sponsored by Scios, the manufacturer of Natrecor.

Manuscript received December 26, 2002; revision accepted March 31, 2003.



*Correspondence to: David R. Williamson, MSc(Pharm), Assistant Professor, Faculté de Pharmacie, Université de Montréal, Hôpital du Sacré-Coeur de Montréal, 5400 Blvd Gouin Ouest, Montréal, QC, H4J 1C5 Canada; e-mail: david.williamson@umontreal.ca*

### BNP

BNP, a 32-amino acid protein, was first isolated from porcine brain.[1] As opposed to ANP and CNP, the BNP amino acid sequence varies greatly among species.[2,3] At physiologic concentrations, these neurohormones play a complex role on body fluid homeostasis and vascular tone.[4] To date, the follow-

ing three natriuretic peptide receptors (NPRs) have been identified: NPR-A; NPR-B; and NPR-C. NPR-A and NPR-B are members of the guanylyl cyclase receptor family and mediate the biological activities of the natriuretic peptides by the synthesis and intracellular accumulation of cyclic guanosine 3′,5′-monophosphate.[5] NPR-C is a clearance receptor for circulating natriuretic peptides and lacks guanylate cyclase activity.[6] Circulating natriuretic peptides also are metabolized by neutral endopeptidase into inactivated fragments.[5] The relative binding affinity of natriuretic peptides to NPRs is illustrated in Table 1.[5]

In humans, BNP is mainly secreted from the heart, and mostly from the ventricles in both healthy individuals and patients with congestive heart failure.[7] Unlike BNP, ANP secretion comes mainly from the atria in healthy individuals, and from both the atria and the ventricles in patients with congestive heart failure. BNP seems to be the only natriuretic peptide that is specific to the ventricles.[8,9] The precursor of BNP, pro-BNP is stored in secretory granules in myocytes. After being synthesized in the ventricle, pro-BNP is cleaved by a protease into its biologically active form, BNP, and N-terminal (NT)-proBNP, the 76-amino acid, the biologically inactive amino portion of pro-BNP.[10] Compared to BNP, NT-proBNP has a longer half-life than the active form of BNP (*ie*, 60 to 120 min vs 15 to 20 min) and is not affected by the administration of exogenous BNP like nesiritide. Finally, animal studies have demonstrated that the gene expression and the ventricular secretion of BNP occur more rapidly than those of ANP in an acute overload, suggesting that BNP may play a role as an "emergency" neurohormone against overload. As a result, BNP could be considered superior to ANP as a potential diagnostic marker of acute heart failure.[11]

In healthy subjects without any cardiovascular disease, BNP levels vary according to sex and age.[12,13] Female subjects demonstrate higher plasma concentrations than male subjects, while BNP levels increase in both sexes with advancing age. This suggests that gender and age should be taken into consideration when defining a normal reference range of BNP for a given patient (Table 2).[12,13]

**Table 1—*Relative Affinity of NPRs to Natriuretic Peptides****

| | Natriuretic Peptides | | |
|---|---|---|---|
| NPRs | ANP | BNP | CNP |
| NPR-A | +++++ | ++++ | |
| NPR-B | | | +++++ |
| NPR-C | +++++ | +++ | +++ |

*+ = degree of affinity.

From a physiologic standpoint, BNP has an important role in congestive heart failure as a counterregulatory hormone to angiotensin II, norepinephrine, and endothelin because it decreases the synthesis of some of these neurohormones and acts like a balance vasodilator (Fig 1). Furthermore, as a result of its hemodynamic effect and its direct tubular action, BNP has natriuretic and diuretic effects. The molecular biology and the physiologic properties of natriuretic peptides and their receptors have been reviewed elsewhere,[4–6] and the reader is invited to consult these publications for further information.

Compared to other neurohormones, plasma BNP concentration correlates in a superior way with pulmonary capillary wedge pressure, left ventricular end-diastolic pressure, and left ventricular ejection fraction in patients with systolic dysfunction.[8,9,14,15] Many studies have shown that in patients with systolic dysfunction, BNP concentration increases with the clinical severity of the disease, as assessed by the New York Heart Association classification. Preliminary data also have demonstrated that BNP could become a powerful predictor of decreased exercise capacity as measured by exercise oxygen uptake in patients with chronic heart failure (CHF).[16] Interestingly, other studies have demonstrated that BNP concentrations also are increased in patients with diastolic dysfunction and left ventricular hypertrophy.[17–19] This indicates that BNP release is increased as left ventricular function deteriorates, and that both increased wall stretch (*ie*, increased volume) and increased tension (*ie*, increased filling pressures) are responsible for this increased secretion.

Because heart failure is a common and costly condition with poor prognosis, new cost-effective strategies must be developed to diagnose heart failure in patients who already have the disease or in those who are at risk of developing it. These strategies could enable early treatment and could prevent, or at least delay, progression to end-stage heart failure. In this respect, BNP plasma levels have the potential to become a practical marker of left ventricular dysfunction in clinical practice.

## BNP as a Diagnostic Tool

### *Acute Care Setting*

In patients presenting to an emergency department with acute dyspnea, a rapid and accurate diagnosis is indispensable in providing adequate treatment. Unfortunately, the signs and symptoms of congestive heart failure are often nonspecific.[20] Although echocardiography is considered to be the

**Table 2—*Impact of Gender and Age on Normal Reference BNP Levels Using the Point-of-Care BNP Test**

| Study | Group | Age, yr | | | | | |
|---|---|---|---|---|---|---|---|
| | | < 35 | 35–44 | 45–54 | 55–64 | 65–74 | > 74 |
| Redfield et al[13] | Women | NA | NA | 18 (10; 32) | 27 (15; 43) | 29 (19; 52) | 67 (28; 89) |
| | Men | NA | NA | 7 (3; 13) | 11 (5; 20) | 18 (7; 37) | 21 (17; 24) |
| Wieczorek et al[25] | Men and women | 7.0 (5; 40) | 8.2 (5; 39) | 13 (5; 38) | 17 (5; 46) | 23 (5; 138) | 23 (5; 135) |

*Values given as median (25th; 75th percentiles). NA = not available.

"gold standard" for the diagnosis of left ventricular dysfunction, it is not readily available in all institutions, it is of limited availability in an urgent care setting, and it represents a costly intervention. Therefore, a rapid and accurate blood test for congestive heart failure would constitute a useful addition to the existing diagnostic tools.

Three preliminary studies have evaluated and demonstrated the usefulness of BNP as a potential diagnostic marker of heart failure in patients presenting with acute dyspnea in the emergency department (Table 3).[21–23] Davis et al[22] evaluated the usefulness of BNP for diagnosing acute decompensated heart failure in 52 patients presenting with acute dyspnea. In this study, BNP was a better diagnostic marker of heart failure than ANP and left ventricular ejection fraction. However, a major limitation of this study was that a time-consuming radioimmunoassay method was used, thus limiting its value in an acute setting. Nonetheless, these results prompted further research[21,23] using a rapid (*ie*, 15 min) point-of-care test for BNP (Triage BNP test; Biosite Diagnostic Inc; San Diego, CA).[21,24] This self-processing fluorescence immunoassay test can quantify BNP by simply adding ethylenediaminetetraacetic acid-anticoagulated whole blood or plasma to the BNP test device, which then is inserted into the metering device for the test. The detection of the assay is 5 to 1,300 pg/mL, with a coefficient of variation for intraassay precision of 9.5 to 13.9% and interassay variation of 10 to 14.8%.[25] The point-of-care BNP test has been shown to have a good correlation with the more time-consuming Shiono radioimmunoassay test (Shionogi; Osaka, Japan)

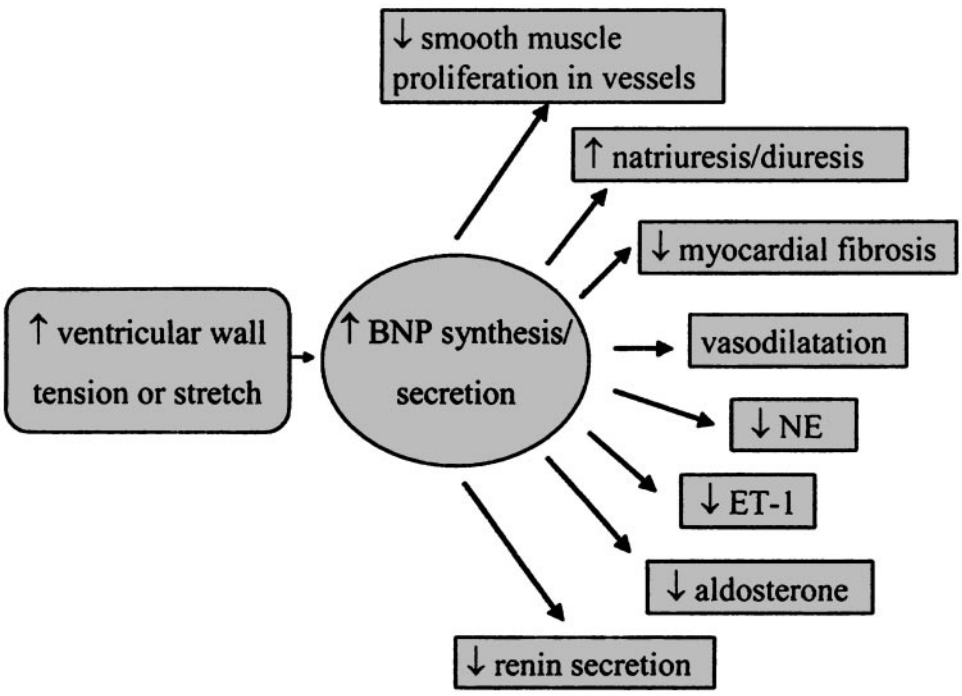



FIGURE 1. Physiology of BNP in congestive heart failure.[4–6,8,10] Following increased ventricular wall tension or stretch, pro-BNP synthesis in the ventricle is increased. Pro-BNP is cleaved by a protease to NT-proBNP (*ie*, the inactive fragment) and BNP. BNP is the biologically active fragment of pro-BNP. The exact role of the various neurohormones on BNP synthesis secretion remains to be clearly established. ET-1 = endothelin-1; NE = norepinephrine.

**Table 3—*Studies Evaluating BNP as a Diagnostic Marker of Heart Failure or Left Ventricular Dysfunction**

| Study | Population/Study Goal | Study Design | Assay Used | Threshold Value, pg/mL | Sens, % | Spec, % | PPV, % | NPV, % | Acc, % |
|---|---|---|---|---|---|---|---|---|---|
| Acute care setting | | | | | | | | | |
| Davis et al[22] | 52 patients/to differentiate LV dysfunction from pulmonary disease | S, O | RIA | 76 | 93 | 90 | NS | NS | NS |
| Dao et al[21] | 250 patients/to diagnose CHF | S, O | FI | 80 | 98 | 92 | 90 | 98 | 95 |
| | | | | 150 | 87 | 97 | 95 | 91 | 93 |
| Morrison et al[23] | 321 patients/to differentiate right or left heart failure from pulmonary disease | S, O | FI | 94 | 86 | 98 | 98 | 83 | 91 |
| | | | | 240 | 96 | 79 | 86 | 93 | 89 |
| Maisel et al[27] | 1,586 patients/to diagnose CHF | M, O | FI | 50 | 97 | 62 | 71 | 96 | 79 |
| | | | | 100 | 90 | 76 | 79 | 89 | 83 |
| Logeart et al[29] | 163 patients/to diagnose CHF | S, O | FI | 80 | 97 | 27 | 76 | 93 | 78 |
| | | | | 200 | 93 | 56 | 83 | 77 | 82 |
| | | | | 300 | 88 | 87 | 94 | 75 | 88 |
| Primary care setting | | | | | | | | | |
| Davidson et al[32] | 87 patients/referred for outpatient ventriculography/to detect LV dysfunction (EF ≤ 35%) | S, O | RIA | 13.8 | NS | NS | 42 | 100 | NS |
| Yamamoto et al[33] | 466 patients/referred for echocardiography/to detect LV systolic dysfunction | S, O | RIA | 37 | | | | | |
| | EF < 45% | | | | 79 | 64 | 21 | 96 | NS |
| | EF < 35% | | | | 90 | 61 | 9.8 | 99.3 | NS |
| Cowie et al[34] | 122 patients referred from general practitioners for suspected heart failure to a heart failure clinic/to confirm the diagnosis of heart failure (according to the European Society of Cardiology) | M, O | RIA | 77 | 97 | 84 | 70 | 98 | NS |
| McDonagh et al[35] | 1,252 patients/aged 25–74 yr old from family physicians' list in the United Kingdom to detect LV systolic dysfunction (EF ≤ 30%) | M, O | RIA | 17.9 | 76 | 87 | 16 | 97.5 | NS |
| Maisel et al[26] | 200 patients/to evaluate presence or absence of systolic LV dysfunction (EF < 50%) or diastolic LV dysfunction by echocardiography | S, O | FI | 38.5 | 95 | 66 | 71 | 93 | 80 |
| | | | | 75 | 86 | 98 | 98 | 89 | 93 |
| Krishnaswamy et al[36] | 400 patients referred for echocardiography/to evaluate LV dysfunction (systolic or diastolic) | S, O | FI | 49 | 91 | 82 | 90 | 85 | 88 |
| | | | | 110 | 75 | 98 | 98 | 70 | 86 |

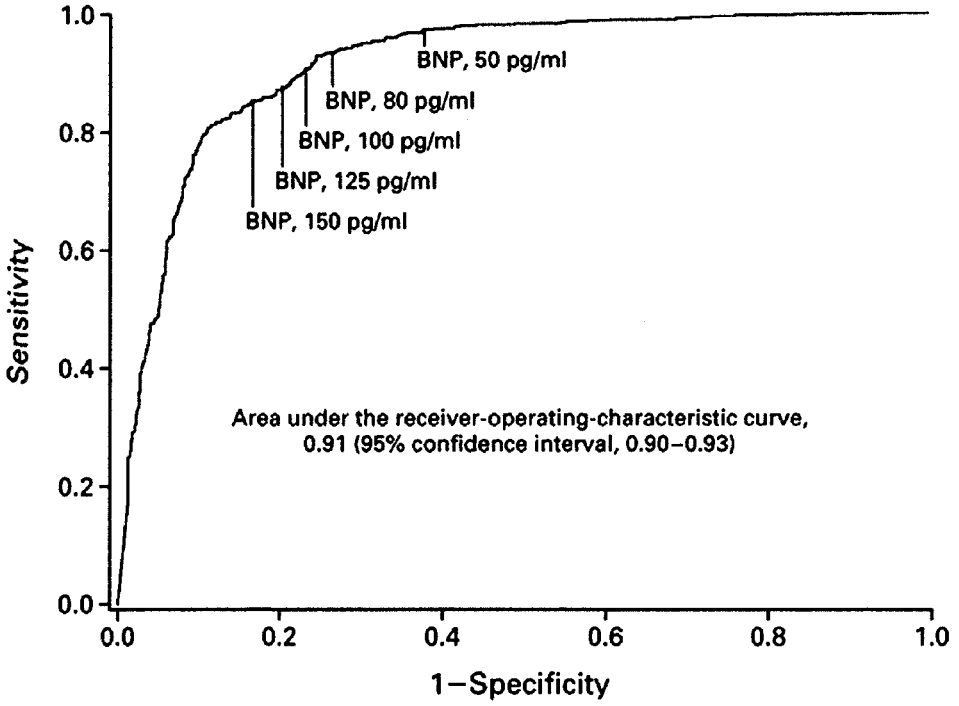
*Acc = accuracy; EF = ejection fraction; FI = fluorescence immunoassay; LV = left ventricular; M = multicenter; NPV = negative predictive value; NS = not specified; PPV = positive predictive value; O = observational; RIA = radioimmunoassay; S = single center; Sens = sensibility; Spec = specificity.

[$R^2 = 0.92$],[26] but demonstrates more variation.[13] This makes the BNP test an acceptable diagnostic test. However, this test is of limited usefulness for clinical research compared to the radioimmunoassay, which has demonstrated less variation and a wider detection range.

Although the results from these studies were impressive, they were performed largely in male veterans and needed confirmation from larger multicenter trials before measurement of plasma BNP levels in the urgent-care setting become the standard of care. The prospective, blinded Breathing Not Properly trial[27] has now corroborated the data obtained in these smaller studies. In that trial, which included 1,586 patients presenting to the emergency department with a primary complaint of shortness of

breath, a BNP plasma level of 100 pg/mL measured by a fluorescence immunoassay had an accuracy of 83.4% to diagnose acute heart failure, as determined by two cardiologists blinded to the BNP plasma levels. A level of 50 pg/mL had a negative predictive value of 96%, again demonstrating that a low BNP plasma level can be used to rule out heart failure in such a setting. Patients with a diagnosis of decompensated heart failure had a mean (± SD) BNP concentration of 675 ± 450 pg/mL, whereas patients with a history of left ventricular dysfunction without decompensated heart failure had a mean BNP concentration of 346 ± 390 pg/mL, and patients without heart failure had a mean BNP concentration of 110 ± 225 pg/mL. In a subsequent analysis of the trial,[28] it was demonstrated that the addition of BNP at a cutoff of 100 pg/mL would have increased the accuracy of the emergency department physician's diagnosis from 74.0 to 81.5% for patients believed to have a high probability of decompensated heart failure. Figure 2 illustrates the capacity of BNP to distinguish between heart failure and other causes of dyspnea in this study. The calculated area under the curve (AUC) of 0.91 compares well with that of the prostate-specific antigen and is far superior to that of Papanicolaou smears or mammography.[27] In a multiple logistic regression analyses of factors used in the diagnosis of heart failure in dyspneic patients, a value for BNP of 100 pg/mL was shown to be the strongest independent predictor of congestive heart failure and to increase the combined explanatory power of the history, signs, symptoms, radiologic findings, and laboratory findings.

A recent single-center trial[29] conducted in 163




| BNP pg/ml | Sensitivity | Specificity | Positive Predictive Value | Negative Predictive Value | Accuracy |
|---|---|---|---|---|---|
| | (95 percent confidence interval) | | | | |
| 50 | 97 (96–98) | 62 (59–66) | 71 (68–74) | 96 (94–97) | 79 |
| 80 | 93 (91–95) | 74 (70–77) | 77 (75–80) | 92 (89–94) | 83 |
| 100 | 90 (88–92) | 76 (73–79) | 79 (76–81) | 89 (87–91) | 83 |
| 125 | 87 (85–90) | 79 (76–82) | 80 (78–83) | 87 (84–89) | 83 |
| 150 | 85 (82–88) | 83 (80–85) | 83 (80–85) | 85 (83–88) | 84 |

FIGURE 2. Receiver-operating characteristic AUC for various cutoff levels of BNP to differentiate between dyspnea due to congestive heart failure and dyspnea due to other causes in the Breathing Not Properly Multinational Study[27] (copyright 2002 Massachusetts Medical Society; all rights reserved; reprinted with permission).

patients compared the diagnostic value of plasma BNP measurement to Doppler echocardiography in patients presenting to the emergency department with severe dyspnea. Similarly to previous trials, a BNP cutoff of 80 pg/mL had a high negative predictive value (93%), while a cutoff of > 300 pg/mL had the highest accuracy (88%) [Table 3]. A "restrictive" mitral inflow pattern (defined as an E-wave/A-wave ratio of > 2, or between 1 and 2 with an E-wave deceleration time of < 130 ms, or a deceleration time of < 130 ms alone in the presence of atrial fibrillation) demonstrated an accuracy of 91% in the 138 patients with assessable Doppler echocardiography findings. Both BNP and Doppler echocardiography added predictive value to clinical variables. A BNP level between 80 and 300 pg/mL had an inferior diagnostic value. In these patients, a restrictive mitral pattern proved to be useful in confirming or ruling out a diagnosis of heart failure.

Therefore, the measurement of BNP levels constitutes an important new addition to the diagnostic tools that are available in patients presenting with acute dyspnea, particularly to exclude the diagnosis of decompensated heart failure. Using the point-of-care BNP test mentioned above (Triage), physicians can rapidly rule out decompensated heart failure when low BNP concentrations (*ie*, < 80 to 100 pg/mL) are measured, whereas high BNP values can confirm a diagnosis of decompensated heart failure.[30] Intermediate values (100 to 400 pg/mL) may not be accurate to confirm a diagnosis of decompensated heart failure, particularly in elderly women (Table 2). Furthermore, such values may only reflect left ventricular dysfunction without decompensation, as illustrated by the mean BNP concentration (346 ± 390 pg/mL) reported in the BNP trial for patients with left ventricular dysfunction without decompensated heart failure.[27] In patients with intermediate BNP values, other potential causes for BNP increases (*eg*, cor pulmonale, pulmonary embolism,[23] or heart failure without exacerbation) should be considered in the interpretation of the BNP concentration and excluded.[30] It is important to stress that clinical judgement should always prevail and that the interpretation of BNP levels should always take into account the global evaluation of a patient. Although the use of this test will in many cases only confirm the diagnosis of heart failure, current data[28] have indicated that the addition of BNP concentrations to clinical variables can markedly improve the diagnostic accuracy of decompensated heart failure.

### *Primary Care Setting*

In the primary care setting, heart failure is also commonly misdiagnosed.[31] Such misdiagnoses can lead to an unacceptable delay in the treatment of heart failure and to excessive referrals for evaluating left ventricular function by echocardiography or radionuclide ventriculography, leading to increased health-care costs. Preliminary data[17] have shown that in a selected population undergoing cardiac catheterization, plasma BNP level measurements could be used to evaluate the need for echocardiography to evaluate left ventricular function. Therefore, many investigators have hypothesized that plasma BNP levels could be used as a screening test for left ventricular dysfunction in the primary care setting in patients who are suspected of having left ventricular dysfunction.

The results of several trials[26,32–36] conducted in various settings evaluating the potential usefulness of BNP as a biochemical marker of heart failure support this conclusion, although using a lower threshold value may be more appropriate to rule out heart failure in the primary care setting (Table 3). Those trials highlighted the superiority of BNP over other neurohormones to detect left ventricular function. Patients with low BNP concentrations (*ie*, < 40 to 50 pg/mL) could be rapidly ruled out from having left ventricular dysfunction, while patients with high BNP concentrations could be referred for further workup to evaluate left ventricular function. Again, a higher discriminatory value may be needed in women and elderly patients. This strategy would result in a decrease in unnecessary referrals for left ventricular function evaluation in patients with symptoms that are suggestive of heart failure and could translate reduced costs.[37]

However, definitive conclusions as to what is the optimal threshold value are difficult to reach because various threshold values of BNP concentrations and definitions of heart failure were used in past studies. Moreover, in some studies,[26,34,36] BNP was used to detect both diastolic and systolic dysfunction, whereas in others[32,33] BNP was used only for systolic dysfunction. Elevated BNP concentrations do not differentiate between diastolic and systolic heart failure,[38] which explains why the diagnostic accuracy of BNP concentrations is increased when both types of ventricular dysfunction are evaluated. This is well-illustrated in a study by Krishnaswamy et al,[36] which demonstrated a superior receiver operating characteristic AUC comparing the sensitivity and specificity of BNP and the echocardiographic diagnosis of both systolic and diastolic dysfunction (AUC, 0.95; 95% confidence interval [CI], 0.93 to 0.97) compared to the echocardiographic diagnosis of systolic dysfunction only (AUC, 0.82; 95% CI, 0.77 to 0.86) or diastolic dysfunction only (AUC, 0.66; 95% CI, 0.61 to 0.72). Future trials should assess the diagnostic role of BNP for both systolic and diastolic

ventricular dysfunction. Because there is no uniform definition for a diagnosis of diastolic dysfunction, some authors have even suggested that an elevated BNP concentration in patients with normal systolic function may become a valuable noninvasive way to diagnose diastolic heart failure.[39] The definition of systolic dysfunction in these trials should be in agreement with that used in clinical trials, which is generally an ejection fraction of ≤ 40%. Use of an improper definition, could result in the exclusion of patients with mild systolic dysfunction who have been shown to benefit from pharmacologic therapy with agents such as angiotensin-converting enzyme (ACE) inhibitors and β-blockers.

The use of BNP[13,35,40] and NT-BNP[10] also has been investigated as a screening tool in the general population for the detection of left ventricular dysfunction, but with conflicting results. Whether this was secondary to discrepancies between the populations studied remains to be determined. Data from a cross-sectional study[41] suggested that a BNP concentration threshold of 50 pg/mL might be efficacious for identifying various cardiac abnormalities, such as atrial fibrillation or flutter, and valvular diseases, and that BNP could be used as an efficient mass screening technique for heart diseases.

At the present time, the use of BNP in the primary care setting seems to be more promising as a tool to rule out heart failure in patients suspected of having left ventricular dysfunction and not as a mass screening tool. Future trials are needed before the use of BNP can be recommended in the primary care setting to determine the most accurate threshold value to rule out left ventricular dysfunction (systolic and diastolic) according to gender and age.[13]

## BNP as a Prognostic Marker

Left ventricular ejection fraction is a prognostic marker of mortality after acute myocardial infarction and in CHF.[42,43] Because plasma BNP concentrations correlate well with left ventricular ejection fraction, many have suggested[8,14,44] that measuring BNP levels in patients after an acute myocardial infarction or with heart failure could become a valuable, noninvasive, easy-to-obtain marker of prognosis.

Preliminary data on the secreting patterns of BNP after ST-elevation myocardial infarction showed an increase in BNP levels on hospital admission, which peaked at about 16 h.[45] Further analysis showed that the time course of BNP levels could be classified into the following two distinct patterns: a monophasic pattern, with one peak approximately 16 h after hospital admission; and a biphasic pattern, with peaks at 16 h and 5 days after hospital admission. The biphasic pattern of secretion was associated with the worst Killip classification, anterior myocardial infarction, and decreased left ventricular function 4 weeks after experiencing myocardial infarction, when compared to the monophasic pattern. This suggests that high BNP concentrations in the days following an acute myocardial infarction may predict a higher risk of ventricular remodeling and a depressed ventricular function. This hypothesis is supported by the work of others[46] and suggests that these patients should be targeted to receive aggressive therapy to reduce ventricular remodeling, such as ACE inhibitors and β-blockers. The initial rapid increase in BNP level also suggests that the synthesis and secretion of BNP may be related to myocardial necrosis, local mechanical stress, or both, and not only to ventricular dysfunction. Experimental data have suggested[47] that increased BNP synthesis originates from both infracted and noninfarcted regions of the ventricle. Many preliminary studies[45,48–51] have demonstrated that plasma BNP levels provide prognostic information that supplements conventional clinical, biochemical, neurohormonal, echocardiographic, and radionuclide ventriculographic evaluation methods (Table 4).

Data from a retrospective analysis of the glycoprotein IIb/IIIa inhibition with Orbofiban in Patients with Unstable coronary Syndromes-Thrombolysis in Myocardial Infarction (TIMI) 16 trial,[52,53] has confirmed that BNP could become a valuable prognostic marker in patients with various types of acute coronary syndrome (ACS). The 10-month mortality rate increased across increasing quartiles of baseline BNP levels before and after adjustment for other independent risks of death, including age, troponin I levels, presence of heart failure, presence of renal failure, and ST deviation (Table 4). The association between mortality rate at 10 months and BNP concentration quartile was significant regardless of the type of ACS. Furthermore, increasing BNP levels remained predictive of the 10-month mortality rate even in patients without troponin I level elevation, suggesting that the prognostic information provided by BNP was independent of myocardial necrosis.[54] These findings were confirmed in a substudy of the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy-TIMI 18 study,[55] which included patients with non-ST-elevation ACS. Finally, similar data for NT-proBNP were observed in a single-center observational study.[56] This study also suggested that different thresholds for predicting adverse outcome according to the different types of ACS may be more appropriate than using a single value. Because no routine measurement of left ventricular function was per-

**Table 4—*Studies of BNP as a Prognostic Marker After an ACS Episode or in Heart Failure**

| Study | Population | Design | Timing of Sampling | Threshold Value, pg/mL | Results |
|---|---|---|---|---|---|
| ACS | | | | | |
| Arakawa et al[48] | 70 consecutive patients with AMI; mean follow-up, 18 mo | S, O | On hospital admission | BNP, 59 | Survival rate was lower in patients with BNP concentration above threshold value as evaluated by Kaplan-Meir analysis ($p < 0.01$) |
| Darbar et al[49] | 75 consecutive patients with AMI; mean follow-up, 19.7 mo | S, O | Between days 2 and 5 post-MI (mean, day 3) | BNP, 69 | Cardiovascular mortality: BNP concentration > 69 pg/mL is a predictor of cardiovascular mortality by univariate analysis; $p = 0.001$ |
| Omland et al[50] | 131 patients with AMI; median follow-up, 1,293 d (CONSENSUS II substudy) | S, O | Day 3 | BNP, 115 | Mortality: comparison between groups using the log-rank test for Kaplan-Meier survival curve for patients below and above threshold ($p < 0.001$) |
| Richards et al[51] | 121 consecutive patients AMI; mean follow-up, 24 mo | S, O | 24–96 h after onset of symptoms | BNP, 103 | Mortality: above threshold, 18 deaths; below threshold, 3 deaths; RR, 5.9; 95% CI, 1.8–19.0; $p < 0.001$ |
| de Lemos et al[53] | 2,525 patients with UA, non-ST and ST-elevation MI (substudy of the OPUS-TIMI 16 trial) | M, O | Median time, 40 ± 20 h | NA | Adjusted OR for 10-mo mortality (vs quartile 1 [5.0–43.6 pg/mL]) |
| | | | | | Quartile 2 (43.7–81.2 pg/mL): OR, 3.8; 95% CI, 1.1–13.3 |
| | | | | | Quartile 3 (81.3–137.8 pg/mL): OR, 4.0; 95% CI, 1.2–13.7 |
| | | | | | Quartile 4 (137.9–1,456.6 pg/mL): OR, 5.8, 95% CI, 1.7–19.7 |
| | | | | BNP, 80 | Adjusted 10-mo mortality: $p = 0.04$ (data not shown) |
| Sabatine et al[55] | 1,635 patients with non-ST-elevation ACS (substudy of the TACTICS-TIMI 18) | M, O | NM | BNP, 80 | 6-mo combined end point of mortality, MI, CHF; OR, 1.6; $p = 0.019$ |
| Omland et al[56] | 609 patients with UA, non-ST and ST-elevation MI | S, O | Median: 3 days | NT-proBNP, 545 pmol/L | All-cause mortality: unadjusted RR, 3.9; 95% CI, 2.4–6.5<br>Adjusted RR, 2.1; 95% CI, 1.1–3.9 |
| CHF | | | | | |
| Tsutamoto et al[57] | 85 clinically stable patients | S, O | NS | BNP, 73 | Survival: survival rate as evaluated by the Kaplan-Meier analysis was lower in patients with BNP concentration above the threshold value ($p < 0.0001$) |
| Koglin et al[60] | 78 CHF patients referred to a heart failure clinic; median follow-up, 398 d | S, O | After optimization of medical therapy | BNP, 107.5 | Free from clinical deterioration or death: estimated freedom from clinical event according to the log-rank/$\chi^2$ statistics was superior in the group of patients with BNP levels below the threshold ($\chi^2 = 32.538$; $p < 0.0001$) |
| Zugck et al[62] | 408 clinically stable patients | S, O | NS | NT-pro BNP | Cardiac death or heart failure, hospitalization: multivariable Cox regression analysis, $\chi^2 = 8.1$; $p = 0.0045$ |
| Berger et al[64] | 452 patients referred to a heart failure clinic | S, O | At the first clinic visit | Log BNP, 2.11 (≈ 130) | Sudden death (mean observation period, 592 ± 387 d); below threshold, 1%, above threshold, 19%; $p = 0.0001$ |
| Richards et al[58] | 415 stable patients with heart failure (substudy of the ANZ carvedilol trial) | M, O | Prior to randomization | BNP, 83 | Mortality: below threshold, 7.3%; above threshold, 15.0%; RR, 2.07; 95% CI, 1.14–3.76 |
| Anand et al[63] | 4,305 patients with stable heart failure, (substudy of Val-HeFT trial) | M, O | At baseline | BNP, 97 | Mortality or morbidity equal or higher vs lower than threshold value: RR, 2.1; 95% CI, 1.79–2.42; $p < 0.0001$ |
| Acute decompensated heart failure | | | | | |
| Maeda et al[59] | 102 patients hospitalized with severe heart failure; mean follow-up, 807 d | S, O | On hospital admission and after 3 mo of treatment | BNP, 170 | Survival: patients with 3-mo BNP plasma levels below the cutoff value had a 3.4 higher rate of survival ($p = 0.0025$); by stepwise multivariate analysis, BNP concentrations at 3 mo following treatment ($p < 0.0001$) but not at baseline ($p = 0.11$) were a predictor of mortality |
| Harrison et al[61] | 325 patients presenting to the ED with dyspnea | S, O | As early as possible following arrival at ED and preceding any treatment | BNP, 230 | CHF event (hospitalization/ED visit or death from CHF): RR, 15.5; 95% CI, 6.2–43.7) |
| | | | | BNP, 480 | CHF event: RR, 8.2; 95% CI, 4.7–14.3 |
| | | | | | Predictive value of a subsequent CHF event: Sens, 68%; Spec, 88%; Acc, 85% |

*AMI = acute myocardial infarction; CI = confidence interval; CONSENSUS II = Cooperative New Scandinavian Enalapril Survival Study II; ED = emergency department; MI = myocardial infarction; NM = not mentioned; NS = not specified; RR = relative risk; OPUS = glycoprotein IIb/IIIa inhibition with Orbofiban in Patients with Unstable coronary Syndromes; TACTICS = Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy; Val-HeFT = Valsartan Heart Failure Trial. See Table 3 for other abbreviations not used in the text.

formed in the first two aforementioned trials,[53,55] more data are required, as a left ventricular dysfunction may have been a confounder to the prognostic importance of BNP in these patients. Further studies also should evaluate whether obtaining repeated BNP or NT-BNP plasma values during the index hospitalization would provide any further prognostic information.

The prognostic value of BNP and NT-proBNP levels also has been assessed in patients with CHF. Several small studies have demonstrated that BNP levels in this context provide prognostic information that supplements conventional clinical, neurohormonal, invasive, and noninvasive evaluations. Selected studies are presented in Table 4.[57–63] Interestingly, BNP seems to be a good predictor not only of death from pump failure, but also from sudden death,[64] thereby suggesting that this neurohormone might become a useful tool in selecting patients who may benefit from an implantable cardioverter-defibrillator. Data from these preliminary studies have now been supported by the analysis of large clinical trials[58,63] (Table 4). Furthermore, current data have suggested that changes in BNP concentrations over time also may be a useful marker of prognosis in patients who have been treated for CHF.[63] Patients with decreasing BNP concentrations would be at a low risk of experiencing an adverse event, while patients with an increasing BNP level would have a higher risk of experiencing an adverse cardiac event.[63] Taken together, this body of evidence suggests that the measurement of BNP concentrations eventually could be used in identifying patients with CHF who require aggressive monitoring and treatment.

Preliminary data[61] also have suggested that obtaining a BNP level at the time of hospital admission for a patient presenting with acute decompensated heart failure also may be of use in predicting outcome (Table 4). Hence, measuring BNP in a patient who presents to the emergency department could be used not only as a diagnostic tool, but also as a prognostic tool in patients in whom acute decompensated heart failure has been diagnosed.

Cheng et al[65] also evaluated the prognostic value of BNP in patients hospitalized for decompensated heart failure using a rapid bedside fluorescence immunoassay test (Biosite Diagnostic Inc; San Diego, CA), but they also measured plasma BNP levels daily. The authors hypothesized that BNP levels would predict outcome (*ie*, death during hospitalization or within 30 days after hospital discharge, or hospital readmission for heart failure within 30 days after hospital discharge). This single-center study included 72 male veterans who had been admitted for congestive heart failure with a New York Heart Association class III or IV determination were included. BNP levels were obtained within 24 h of hospital admission and then daily until hospital discharge or death. Patients who died or were readmitted to the hospital within 30 days tended to have an increase in BNP concentrations during hospitalization (increase, 239 ± 233 pg/mL) compared to patients with successful treatment, who showed a decrease in BNP levels (decrease, 216 ± 69 pg/mL; $p < 0.05$). By univariate analysis, the BNP level that was measured last was strongly associated with patients experiencing one of the prespecified outcomes ($p < 0.0001$). Larger trials are required to confirm these findings before the daily measuring of BNP levels becomes part of clinical practice in patients with acute decompensated heart failure.

These studies and others[49,66,67] have demonstrated that BNP could constitute an important new marker of prognosis in patients with CHF, as current data have suggested that its use increases the prognostic information obtained by clinical, biochemical, echocardiographic, or invasive methods. Future trials need to corroborate the findings of previously published reports and to define clearly a threshold for identifying patients that are at higher risk of an adverse event. The data regarding the use of plasma BNP as a marker of prognosis in patients with acute decompensated heart failure is at this point insufficient and requires confirmation by larger studies before it can be incorporated into clinical practice. Furthermore, additional data are required before the measurement of BNP becomes part of clinical practice in patients with ACS, more precisely, clear thresholds according to ACS to predict outcome and whether any particularly therapeutic intervention provides any particular benefit to these high-risk patients.

## BNP as a Marker for Tailored Therapy

ACE inhibitors, β-blockers, and spironolactone all have been demonstrated to reduce mortality and morbidity in patients experiencing congestive heart failure.[68–73] These agents, along with diuretics, constitute the cornerstone of treatment for congestive heart failure.[74] Although these agents reduce mortality in the overall population, interpatient variability, whether racial[74–76] or genetic,[77,78] precludes uniform dosing and may not allow equal benefit in all individuals.

Current heart failure treatment strategies do not take into account the plasma concentration of neurohormones, even though several of these substances have been shown to be independent markers of left ventricular ejection fraction and mortality in patients

with heart failure.[57,79,80] However, several studies have evaluated the effect of drugs used in the management of heart failure on BNP levels. Compared to placebo, ACE inhibitors, angiotensin II receptor blockers, and their combination were shown to reduce BNP levels in a dose-dependent manner in the acute phase and after long-term therapy in patients with left ventricular dysfunction.[81–88] This decrease in BNP levels probably resulted from a beneficial reduction in cardiac ventricular filling pressure and cardiac remodeling produced by the inhibition of the renin-angiotensin system.

Reductions in BNP levels also were reported following long-term treatment with β-blockers, while a temporary increase in BNP levels was observed in the short term,[89–92] although some studies have shown discrepancies.[71] The decrease in BNP levels observed with β-blocker therapy has been shown[92] to correlate with improvement in left ventricular ejection fraction. Moreover, in a retrospective analysis of the Australia-New Zealand Heart Failure Group,[58] patients with increased baseline BNP levels showed the greatest benefits from carvedilol. Therefore, more definitive data regarding the impact of β-blockers are needed.

Spironolactone administration also has resulted in a significant decrease in BNP levels.[93,94] The impact of digoxin therapy on BNP levels has not been extensively studied. One dose of IV deslanoside, a digitalis glycoside, was shown to increase BNP levels.[95] The mechanism for this increase is uncertain. To date, the impact of digoxin on BNP levels has not been evaluated in patients with heart failure.

Based on the hypothesis that BNP plasma levels could reflect the level of therapeutic success, a preliminary study by Murdoch et al[96] sought to determine whether titration of vasodilator therapy, specifically ACE inhibitors, according to BNP levels could be of value in optimizing individual treatment in patients with heart failure. Although results showed some favorable hemodynamic trends, few conclusions could be drawn from this small underpowered study.

In a larger study by Troughton et al,[97] 69 patients with mild-to-moderate heart failure (*ie*, mean left ventricular ejection fraction, 27%) who had been hospitalized for decompensated heart failure were randomized, in a double-blind fashion, to treatment guided either by plasma NT-proBNP, or by clinical assessment alone, after an initial stabilization. Treatment was intensified to reduce NT-proBNP levels to $< 200$ pmol/L in the BNP group and to obtain clinically compensated heart failure in the clinical group. The mean follow-up period was 9.6 months. The primary end point of total cardiovascular events (*ie*, cardiovascular death, hospital admission, or outpatient decompensated heart failure) was significantly lower in the BNP group than in the clinical group (19 vs 54 events; $p = 0.02$). One death occurred in the BNP group, and seven deaths occurred in the clinical group ($p = 0.06$). The time to first event analyzed by Kaplan-Meier curves showed significant divergence by 6 months ($p = 0.034$). Although the results from this study are impressive, a larger scale trial would need to be performed to confirm this promising new avenue of treatment before such tailored therapy becomes the standard of care. Emerging data also have suggested that such a strategy may be helpful in the treatment of acute decompensated heart failure.[98]

## Emerging Roles of BNP

Preliminary data have suggested that BNP could be a useful marker of right ventricular dysfunction and outcome in patients with pulmonary hypertension,[99–101] congenital heart disease,[102] pulmonary embolism,[103] and chronic respiratory diseases.[104–106] In addition, BNP concentrations could become a potential marker of efficacy following pulmonary thromboendarterectomy[101,107] or vasodilator therapy in patients with chronic thromboembolic pulmonary hypertension[107] and primary pulmonary hypertension,[100] or in identifying patients with pulmonary embolism at high risk of right ventricular failure, who require more aggressive monitoring and treatment.[103] Further data are needed before considering measuring BNP concentrations in these settings. Furthermore, data are required to know whether or not BNP will be of any clinical relevance in these patients if left ventricular dysfunction is present. Other potential uses of measuring plasma BNP levels could be the detection of early cardiotoxicity of certain drugs like the antineoplastic agent antracycline[108,109] and the prediction of outcome in patients following a heart transplantation.[110]

### *BNP as a Drug*

Nesiritide (Natrecor; Scios; Sunnyvale, CA) is the human recombinant form of BNP and produces the same actions as endogenous BNP. It has been evaluated and is indicated in patients with acute heart failure who have dyspnea at rest or with minimal activity.[111] Preliminary studies in patients with heart failure showed that the IV administration of nesiritide produces dose-dependent vasodilatation,[112–115] which is mediated by the activation of the cyclic guanosine 3′,5′-monophosphate-coupled receptor NPR-A that is present on the surface of vascular smooth muscle cells.[4] Nesiritide is an arte-

rial and venous vasodilator, as demonstrated by a decrease in both pulmonary capillary wedge pressure and peripheral vascular resistance, although significant arterial vasodilatation is seen only at high doses (Table 5).[112,113,115–117] This results in an increase in stroke volume and cardiac index. Because nesiritide does not increase heart rate, does not have any positive inotropic effect, and may produce a vasodilatory effect on epicardial vessels, it probably has a beneficial effect on myocardial oxygen consumption.[118] It has a rapid onset of action after bolus administration (< 15 min) and a short half-life (bicompartmental model: $t_{1/2}\alpha = 10$ min; $t_{1/2}\beta = 15$ min), which allow easy titration.[113,116,117]

Nesiritide infusion also decreases plasma aldosterone levels while producing no effect on renin levels, which suggests a direct inhibitory effect on the adrenal glands.[112,119] This is in contrast with nitroprusside, which has recently been shown[98] to increase aldosterone levels in patients with acute heart failure. At physiologic levels, IV infusion of BNP produces a sympathoinhibitory effect, while the sympathetic nervous activity is not affected by therapeutic doses, despite an anticipated reflex sympathetic increase secondary to a decrease in filling and arterial pressures.[120] IV administration of nesiritide also decreases plasma levels of endothelin-1.[121] In addition, BNP increases urine volume and sodium excretion, effects that are more pronounced in patients with congestive heart failure than in healthy subjects and results in a diuretic-sparing effect.[112] Whether these effects are secondary to improved hemody-

**Table 5—*Hemodynamic Changes From Clinical Trials of Nesiritide in Patients With Acute CHF****

| Study/Design/Duration of Infusion | Agent/Dose | Time of Measurement, h | PCWP, mm Hg | RAP, mm Hg | SVR, dyne · s · cm$^{-5}$ | CI, L/min/m$^2$ | PVR, dyne · s · cm$^{-5}$ | SBP, mm Hg | HR, beats/min |
|---|---|---|---|---|---|---|---|---|---|
| Mills et al[115]/ R, D, P, M/24 h | Placebo (n = 29) | 3 | − 1.8† | − 0.8 | − 16 | 0 | NA | + 1.2 | + 2.6 |
| | | 24 | − 1.8 | − 1.4 | − 18 | + 0.1 | NA | + 2.1 | + 4.5 |
| | Nesiritide/B, 0.25 μg/kg; I, 0.015 μg/kg/min (n = 22) | 3 | − 8.9†‡ | − 3.7†‡ | − 364† | + 0.4†‡ | NA | − 7.4†‡ | − 3.7†‡ |
| | | 24 | − 8.3†‡ | − 2.6† | − 284 | + 0.2† | NA | − 6.1†‡ | − 1.0‡ |
| | Nesiritide/B, 0.5 μg/kg; I, 0.03 μg/kg/min (n = 26) | 3 | − 6.0†‡ | − 3.3†‡ | − 204† | + 0.3† | NA | − 4.3 | − 2.2 |
| | | 24 | − 3.7† | − 3.6† | − 67 | 0 | NA | − 3.3 | − 0.2 |
| | Nesiritide/B, 1.0 μg/kg; I, 0.6 μg/kg/min (n = 26) | 3 | − 10.8†‡ | − 4.5†‡ | − 500†‡ | + 0.7†‡ | NA | − 10.0†‡ | + 6.2† |
| | | 24 | − 8.4†‡ | − 2.9† | − 355† | +0.4†‡ | NA | − 9.0†‡ | + 4.0† |
| Colucci et al[112]/ R, D, P, M/ at least 6 h | Placebo (n = 42) | 6 | + 2.0 | + 0.4 | + 161 | − 0.1 | + 26 | + 0.3 | + 1.4 |
| | Nesiritide/B, 0.3 μg/kg; I, 0.015 μg/kg/min (n = 43) | | − 6.0‡ | − 2.6‡ | − 247‡ | +0.2‡ | − 62 | − 4.4 | − 1.6 |
| | Nesiritide/B, 0.6 μg/kg; I, 0.03 μg/kg/min (n = 42) | | − 9.6‡ | − 5.1‡ | − 347‡ | + 0.4‡ | − 2 | − 9.3‡ | 0 |
| VMAC[116]/R, D, P, M (minimum, 24 h median, 25 h) | Placebo (n = 62) | 3 | − 2 | 0 | − 44 | 0 | + 21 | − 2.5 | NA |
| | Nitroglycerin/I, per investigator (mean at 3 h, 42 μg/min) [n = 60] | 3 | − 3.8 | − 2.6‡ | − 105 | + 0.2 | − 18 | − 5.7 | NA |
| | Nesiritide/B, 2 μg/kg; I, 0.01 μg/kg/min (n = 62) | 3 | − 5.8‡§ | − 3.1‡ | − 144 | + 0.1 | − 21‡ | − 5.6‡ | NA |

*B = bolus; CI = cardiac index; D = double-blind; HR = heart rate; I = infusion; NA = not applicable; O = open; P = placebo-controlled; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; R = randomized; RAP = right atrial pressure; SBP = systolic BP; SVR = systemic vascular resistance. See Table 3 for abbreviations not used in the text.

†$p < 0.05$ (vs baseline).

‡$p < 0.05$ (vs placebo).

§$p < 0.05$ (vs nitroglycerin).

namics, a direct action, aldosterone suppression or a combination of these effects remains to be established.

Few studies with clinical end points have been published with nesiritide. Published trials were mainly powered to assess hemodynamic response and symptom relief with nesiritide. IV nesiritide was demonstrated to improve symptoms in patients with acute decompensated heart failure compared to placebo[112,116] and to a similar extent than commonly used vasoactive agents[112] such as nitroglycerin.[116] As seen with other vasodilators, symptom relief is probably due in part to a decrease in mitral regurgitation following a decrease in left ventricular end-diastolic volume, and an increase in forward stroke volume resulting in a decrease in regurgitation flow and volume.[122,123]

Subsequent analysis of two of these trials[110,112,124] revealed that nesiritide produced less sustained ventricular tachycardia ($p = 0.014$), nonsustained ventricular tachycardia ($p = 0.029$), and cardiac arrest ($p = 0.011$) than dobutamine,[125] and that nesiritide may improve survival compared to the latter (dobutamine, 31%; nesiritide [0.015 μg/kg/min] 18% [$p < 0.05$]; dobutamine vs nesiritide [0.03 μg/kg/min], 24%; difference not significant).[126]

Current dosing recommendations are based on those used in the multicenter Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial.[116] In this trial, 489 patients with dyspnea at rest and hospitalized for acutely decompensated heart failure were randomized to nesiritide, nitroglycerin, or placebo in addition to standard therapy in a double-blind fashion.[116] Randomized patients were stratified according to the use of a right heart catheter ($n = 246$) or not ($n = 243$). Patients included in the catheterized group were randomized to placebo, IV nitroglycerin (at a dose determined by the investigator), nesiritide fixed-dose (a bolus of 2 μg/kg followed by an infusion of 0.01 μg/kg/min), or nesiritide adjustable-dose. In this latter group, the same initial regimen as in the fixed-dose arm was used. Additional dose increments of a bolus of 1 μg/kg followed by an increase in infusion rate of 0.005 μg/kg/min with a maximum infusion rate of 0.03 μg/kg/min could be performed following the first 3 h and at an interval of 3 h if the systolic BP was ≥ 100 mm Hg and pulmonary capillary wedge pressure was ≥ 20 mm Hg. Noncatheterized patients were randomized in a similar manner, except there was no nesiritide adjustable-dose group. Higher doses should be avoided because of the increased risk of hypotension.[115] In both groups, patients treated with placebo were randomized to nesiritide fixed-dose or nitroglycerin after 3 h. Nesiritide had hemodynamic effects similar to nitroglycerin, with the exception of a lower decrease in pulmonary capillary wedge pressure. This may be the result of improper dosing of nitroglycerin in this trial as the mean dose was only 42 μg/min in catheterized patients after 3 h and 29 μg/min in noncatheterized patients. No difference in improvement of dyspnea was seen compared to that with nitroglycerin in the overall population. Although not powered to measure such end points, nesiritide therapy resulted in no benefit regarding the 7-day or 6-month mortality rate compared to nitroglycerin therapy. Treatment with nesiritide is very well-tolerated, with hypotension being the only significant adverse drug reaction.

Therefore, nesiritide has revealed itself as a unique agent in the management of decompensated heart failure. Unlike nitroglycerin, its use has not been associated with tolerance to its hemodynamic effects, although experience is limited with infusion lasting $> 72$ h (6% of patients in the VMAC trial received nesiritide for $> 72$ h). Compared to nitroprusside, the use of nesiritide is not accompanied by an increased risk of thiocyanate or cyanide toxicity in patients with renal or hepatic dysfunction, respectively, and nesiritide seems to have a more positive effect on neurohormonal activation.[98,112] Finally, the hemodynamic improvements seen with nesiritide therapy are not secondary to increases in intracellular cyclic AMP and calcium, as has been seen with the use of positive inotropes such as dobutamine, and therefore the use of nesiritide does not result in any increased risk of ventricular arrhythmias.[125]

No guidelines currently exist regarding the treatment of acute decompensated heart failure. Diuretic agents, as a monotherapy or in combination, are generally considered to be the cornerstone of the treatment of fluid-overloaded patients.[127,128] The use of IV vasodilators and positive inotropes in combination with diuretics also has been recommended in selected patients.[127,128] Despite this, the impact on clinical outcome of agents used in the management of decompensated heart failure, other than symptom relief and improving hemodynamic parameters, remains unclear. Similar data are also lacking regarding nesiritide. Therefore, despite its uniqueness, prospective data demonstrating an improved clinical outcome are needed to justify the increased cost of nesiritide in the management of acute decompensated heart failure, particularly in view of the disappointing results of the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events,[129] which showed no benefit for the use of omapatrilat, a drug with both ACE-inhibiting properties and neutral endopeptidase-inhibiting properties, the enzyme responsible for the breakdown of natriuretic peptides, compared to enalapril in the long-term management of heart failure.

## Conclusions

BNP, a natriuretic peptide, is produced and released from the ventricles in response to increased wall stretch and tension. The measurement of BNP concentrations has become a useful tool in the diagnosis of acute heart failure in patients presenting to an emergency department with acute dyspnea. Its role in the primary care setting remains to be clearly established. Because BNP does not differentiate between systolic and diastolic dysfunction and does not provide any information regarding valvular integrity or function, it is important to underline that BNP will not replace the need to perform echocardiography, but rather will serve as a complementary tool. In the future, BNP concentrations also could become an important marker of prognosis for patients with congestive heart failure or those who have experienced an ACS episode, and could become a new avenue in tailoring therapy in patients with heart failure. Finally, nesiritide, the human recombinant form of BNP, has become a new tool in the armamentarium for the management of acute heart failure that demonstrates several potential advantages over current drug therapies. There is a need for additional data on clinical outcome (*ie*, mortality, rehospitalization, and length of stay) to justify the increased cost related to the use of nesiritide in the management of patients with decompensated heart failure.

## References


1 Sudoh T, Kangawa K, Minamino N, et al. A new natriuretic peptide in porcine brain. Nature 1988; 332:78–81
2 Sudoh T, Maekawa K, Kojima M, et al. Cloning and sequence analysis of cDNA encoding a precursor for human brain natriuretic peptide. Biochem Biophys Res Commun 1989; 159:1427–1434
3 Porter JG, Arfsten A, Palisi T, et al. Cloning of a cDNA encoding porcine brain natriuretic peptide. J Biol Chem 1989; 264:6689–6692
4 Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998; 339:321–328
5 Koller KJ, Goeddel DV. Molecular biology of the natriuretic peptides and their receptors. Circulation 1992; 86:1081–1088
6 Stein BC, Levin RI. Natriuretic peptides: physiology, therapeutic potential, and risk stratification in ischemic heart disease. Am Heart J 1998; 135:914–923
7 Mukoyama M, Nakao K, Saito Y, et al. Increased human brain natriuretic peptide in congestive heart failure. N Engl J Med 1990; 323:757–758
8 Yoshimura M, Yasue H, Okumura K, et al. Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart failure. Circulation 1993; 87:464–469
9 Yasue H, Obata K, Okumura K, et al. Increased secretion of atrial natriuretic polypeptide from the left ventricle in patients with dilated cardiomyopathy. J Clin Invest 1989; 83:46–51
10 Hobbs FD, Davis RC, Roalfe AK, et al. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. BMJ 2002; 324:1498
11 Nakagawa O, Ogawa Y, Itoh H, et al. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy: evidence for brain natriuretic peptide as an "emergency" cardiac hormone against ventricular overload. J Clin Invest 1995; 96:1280–1287
12 Wang TJ, Larson MG, Levy D, et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. Am J Cardiol 2002; 90:254–258
13 Redfield MM, Rodeheffer RJ, Jacobsen SJ, et al. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 2002; 40:976–982
14 Wei CM, Heublein DM, Perrella MA, et al. Natriuretic peptide system in human heart failure. Circulation 1993; 88:1004–1009
15 Maeda K, Tsutamoto T, Wada A, et al. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J 1998; 135:825–832
16 Kruger S, Graf J, Kunz D, et al. Brain natriuretic peptide levels predict functional capacity in patients with chronic heart failure. J Am Coll Cardiol 2002; 40:718–722
17 Yamamoto K, Burnett JC Jr, Jougasaki M, et al. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. Hypertension 1996; 28:988–994
18 Ogawa T, Linz W, Stevenson M, et al. Evidence for load-dependent and load-independent determinants of cardiac natriuretic peptide production. Circulation 1996; 93: 2059–2067
19 Hasegawa K, Fujiwara H, Doyama K, et al. Ventricular expression of brain natriuretic peptide in hypertrophic cardiomyopathy. Circulation 1993; 88:372–380
20 Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA 1989; 261:884–888
21 Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol 2001; 37:379–385
22 Davis M, Espiner E, Richards G, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. Lancet 1994; 343:440–444
23 Morrison LK, Harrison A, Krishnaswamy P, et al. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. J Am Coll Cardiol 2002; 39:202–209
24 Vogeser M, Jacob K. B-type natriuretic peptide (BNP): validation of an immediate response assay. Clin Lab 2001; 47:29–33
25 Wieczorek SJ, Wu AH, Christenson R, et al. A rapid B-type natriuretic peptide assay accurately diagnoses left ventricular dysfunction and heart failure: a multicenter evaluation. Am Heart J 2002; 144:834–839
26 Maisel AS, Koon J, Krishnaswamy P, et al. Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. Am Heart J 2001; 141: 367–374
27 Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347:161–167

28 McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. Circulation 2002; 106: 416–422
29 Logeart D, Saudubray C, Beyne P, et al. Comparative value of Doppler echocardiography and B-type natriuretic peptide assay in the etiologic diagnosis of acute dyspnea. J Am Coll Cardiol 2002; 40:1794–1800
30 Maisel A. B-type natriuretic peptide levels: diagnostic and prognostic in congestive heart failure: what's next? Circulation 2002; 105:2328–2331
31 Remes J, Miettinen H, Reunanen A, et al. Validity of clinical diagnosis of heart failure in primary health care. Eur Heart J 1991; 12:315–321
32 Davidson NC, Naas AA, Hanson JK, et al. Comparison of atrial natriuretic peptide B-type natriuretic peptide, and N-terminal proatrial natriuretic peptide as indicators of left ventricular systolic dysfunction. Am J Cardiol 1996; 77:828–831
33 Yamamoto K, Burnett JC Jr, Bermudez EA, et al. Clinical criteria and biochemical markers for the detection of systolic dysfunction. J Card Fail 2000; 6:194–200
34 Cowie MR, Struthers AD, Wood DA, et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 1997; 350:1349–1353
35 McDonagh TA, Robb SD, Murdoch DR, et al. Biochemical detection of left-ventricular systolic dysfunction. Lancet 1998; 351:9–13
36 Krishnaswamy P, Lubien E, Clopton P, et al. Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction. Am J Med 2001; 111:274–279
37 Nielsen OW, McDonagh TA, Robb SD, et al. Retrospective analysis of the cost-effectiveness of using plasmabrain natriuretic peptide in screening for left ventricular systolic dysfunction in the general population. J Am Coll Cardiol 2003; 41:113–120
38 Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002; 288:2144–2150
39 Lubien E, DeMaria A, Krishnaswamy P, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. Circulation 2002; 105:595–601
40 Vasan RS, Benjamin EJ, Larson MG, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. JAMA 2002; 288:1252–1259
41 Nakamura M, Endo H, Nasu M, et al. Value of plasma B type natriuretic peptide measurement for heart disease screening in a Japanese population. Heart 2002; 87:131–135
42 Cohn JN, Johnson GR, Shabetai R, et al. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure: the V-HeFT VA Cooperative Studies Group. Circulation 1993; 87:VI5–VI6
43 White HD, Norris RM, Brown MA, et al. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987; 76:44–51
44 Naruse M, Takeyama Y, Tanabe A, et al. Atrial and brain natriuretic peptides in cardiovascular diseases. Hypertension 1994; 23:I231–I234
45 Morita E, Yasue H, Yoshimura M, et al. Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. Circulation 1993; 88:82–91
46 Nagaya N, Nishikimi T, Goto Y, et al. Plasma brain natriuretic peptide is a biochemical marker for the prediction of progressive ventricular remodeling after acute myocardial infarction. Am Heart J 1998; 135:21–28
47 Hama N, Itoh H, Shirakami G, et al. Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction. Circulation 1995; 92:1558–1564
48 Arakawa N, Nakamura M, Aoki H, et al. Plasma brain natriuretic peptide concentrations predict survival after acute myocardial infarction. J Am Coll Cardiol 1996; 27: 1656–1661
49 Darbar D, Davidson NC, Gillespie N, et al. Diagnostic value of B-type natriuretic peptide concentrations in patients with acute myocardial infarction. Am J Cardiol 1996; 78:284–287
50 Omland T, Aakvaag A, Bonarjee VV, et al. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction: comparison with plasma atrial natriuretic peptide and N-terminal proatrial natriuretic peptide. Circulation 1996; 93:1963–1969
51 Richards AM, Nicholls MG, Yandle TG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. Circulation 1998; 97:1921–1929
52 Cannon CP, McCabe CH, Wilcox RG, et al. Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. Circulation 2000; 102:149–156
53 de Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med 2001; 345:1014–1021
54 Rabbani LE. Acute coronary syndromes–beyond myocyte necrosis. N Engl J Med 2001; 345:1057–1059
55 Sabatine MS, Morrow DA, de Lemos JA, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation 2002; 105:1760–1763
56 Omland T, Persson A, Ng L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. Circulation 2002; 106:2913–2918
57 Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 1997; 96:509–516
58 Richards AM, Doughty R, Nicholls MG, et al. Neurohumoral prediction of benefit from carvedilol in ischemic left ventricular dysfunction: Australia-New Zealand Heart Failure Group. Circulation 1999; 99:786–792
59 Maeda K, Tsutamoto T, Wada A, et al. High levels of plasma brain natriuretic peptide and interleukin-6 after optimized treatment for heart failure are independent risk factors for morbidity and mortality in patients with congestive heart failure. J Am Coll Cardiol 2000; 36:1587–1593
60 Koglin J, Pehlivanli S, Schwaiblmair M, et al. Role of brain natriuretic peptide in risk stratification of patients with congestive heart failure. J Am Coll Cardiol 2001; 38:1934–1941

61 Harrison A, Morrison LK, Krishnaswamy P, et al. B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. Ann Emerg Med 2002; 39:131–138
62 Zugck C, Haunstetter A, Kruger C, et al. Impact of beta-blocker treatment on the prognostic value of currently used risk predictors in congestive heart failure. J Am Coll Cardiol 2002; 39:1615–1622
63 Anand I, Fisher LD, Chiang YT, et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2003; 107:1278–1283
64 Berger R, Huelsman M, Strecker K, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. Circulation 2002; 105:2392–2397
65 Cheng V, Kazanagra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. J Am Coll Cardiol 2001; 37:386–391
66 Richards AM, Nicholls MG, Yandle TG, et al. Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction: The Christchurch Cardioendocrine Research Group. Heart 1999; 81:114–120
67 Choy AM, Darbar D, Lang CC, et al. Detection of left ventricular dysfunction after acute myocardial infarction: comparison of clinical, echocardiographic, and neurohormonal methods. Br Heart J 1994; 72:16–22
68 The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316:1429–1435
69 The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991; 325:293–302
70 The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999; 353:9–13
71 The RESOLVD Investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy: the randomized evaluation of strategies for left ventricular dysfunction pilot study. Circulation. 2000; 101:378–384
72 Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341:709–717
73 Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344:1651–1658
74 Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary; a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2001; 38:2101–2113
75 Yancy CW, Fowler MB, Colucci WS, et al. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. N Engl J Med 2001; 344:1358–1365
76 Exner DV, Dries DL, Domanski MJ, et al. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. N Engl J Med 2001; 344:1351–1357
77 Cicoira M, Zanolla L, Rossi A, et al. Failure of aldosterone suppression despite angiotensin-converting enzyme (ACE) inhibitor administration in chronic heart failure is associated with ACE DD genotype. J Am Coll Cardiol 2001; 37:1808–1812
78 McNamara DM, Holubkov R, Janosko K, et al. Pharmacogenetic interactions between beta-blocker therapy and the angiotensin-converting enzyme deletion polymorphism in patients with congestive heart failure. Circulation 2001; 103:1644–1648
79 Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984; 311:819–823
80 Hulsmann M, Stanek B, Frey B, et al. Value of cardiopulmonary exercise testing and big endothelin plasma levels to predict short-term prognosis of patients with chronic heart failure. J Am Coll Cardiol 1998; 32:1695–1700
81 Motwani JG, McAlpine H, Kennedy N, et al. Plasma brain natriuretic peptide as an indicator for angiotensin-converting-enzyme inhibition after myocardial infarction. Lancet 1993; 341:1109–1113
82 Yasuda S, Goto Y, Sumida H, et al. Angiotensin-converting enzyme inhibition restores hepatocyte growth factor production in patients with congestive heart failure. Hypertension 1999; 33:1374–1378
83 Yoshimura M, Yasue H, Tanaka H, et al. Responses of plasma concentrations of A type natriuretic peptide and B type natriuretic peptide to alacepril, an angiotensin-converting enzyme inhibitor, in patients with congestive heart failure. Br Heart J 1994; 72:528–533
84 van Veldhuisen DJ, Genth-Zotz S, Brouwer J, et al. High-versus low-dose ACE inhibition in chronic heart failure: a double-blind, placebo-controlled study of imidapril. J Am Coll Cardiol 1998; 32:1811–1818
85 Brunner-La Rocca HP, Weilenmann D, Kiowski W, et al. Within-patient comparison of effects of different dosages of enalapril on functional capacity and neurohormone levels in patients with chronic heart failure. Am Heart J 1999; 138:654–662
86 Tsutamoto T, Wada A, Maeda K, et al. Angiotensin II type 1 receptor antagonist decreases plasma levels of tumor necrosis factor alpha, interleukin-6 and soluble adhesion molecules in patients with chronic heart failure. J Am Coll Cardiol 2000; 35:714–721
87 McKelvie RS, Yusuf S, Pericak D, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study: the RESOLVD Pilot Study Investigators. Circulation 1999; 100: 1056–1064
88 Latini R, Masson S, Anand I, et al. Effects of valsartan on circulating brain natriuretic peptide and norepinephrine in symptomatic chronic heart failure: the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2002; 106:2454–2458
89 Sanderson JE, Chan WW, Hung YT, et al. Effect of low dose beta blockers on atrial and ventricular (B type) natriuretic factor in heart failure: a double blind, randomised comparison of metoprolol and a third generation vasodilating beta blocker. Br Heart J 1995; 74:502–507
90 Hara Y, Hamada M, Shigematsu Y, et al. Effect of beta-blocker on left ventricular function and natriuretic peptides in patients with chronic heart failure treated with angiotensin-converting enzyme inhibitor. Jpn Circ J 2000; 64:365–369
91 Fujimura M, Yasumura Y, Ishida Y, et al. Improvement in left ventricular function in response to carvedilol is accompanied by attenuation of neurohumoral activation in patients with dilated cardiomyopathy. J Card Fail 2000; 6:3–10
92 Kawai K, Hata K, Takaoka H, et al. Plasma brain natriuretic peptide as a novel therapeutic indicator in idiopathic dilated cardiomyopathy during beta-blocker therapy: a potential of hormone-guided treatment. Am Heart J 2001; 141:925–932

93 Tsutamoto T, Wada A, Maeda K, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. J Am Coll Cardiol 2001; 37:1228–1233
94 Rousseau MF, Gurne O, Duprez D, et al. Beneficial neurohormonal profile of spironolactone in severe congestive heart failure: results from the RALES neurohormonal substudy. J Am Coll Cardiol 2002; 40:1596–1601
95 Tsutamoto T, Wada A, Maeda K, et al. Digitalis increases brain natriuretic peptide in patients with severe congestive heart failure. Am Heart J 1997; 134:910–916
96 Murdoch DR, McDonagh TA, Byrne J, et al. Titration of vasodilator therapy in chronic heart failure according to plasma brain natriuretic peptide concentration: randomized comparison of the neurodynamic and neuroendocrine effects of tailored versus empirical therapy. Am Heart J 1999; 138:1126–1132
97 Troughton RW, Frampton CM, Yandle TG, et al. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000; 355:1126–1130
98 Johnson W, Omland T, Hall C, et al. Neurohormonal activation rapidly decreases after intravenous therapy with diuretics and vasodilators for class IV heart failure. J Am Coll Cardiol 2002; 39:1623–1629
99 Nagaya N, Nishikimi T, Okano Y, et al. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 1998; 31:202–208
100 Nagaya N, Nishikimi T, Uematsu M, et al. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation 2000; 102: 865–870
101 Nagaya N, Ando M, Oya H, et al. Plasma brain natriuretic peptide as a noninvasive marker for efficacy of pulmonary thromboendarterectomy. Ann Thorac Surg 2002; 74:180–184
102 Tulevski II, Groenink M, van Der Wall EE, et al. Increased brain and atrial natriuretic peptides in patients with chronic right ventricular pressure overload: correlation between plasma neurohormones and right ventricular dysfunction. Heart 2001; 86:27–30
103 Tulevski II, Hirsch A, Sanson BJ, et al. Increased brain natriuretic peptide as a marker for right ventricular dysfunction in acute pulmonary embolism. Thromb Haemost 2001; 86:1193–1196
104 Bando M, Ishii Y, Sugiyama Y, et al. Elevated plasma brain natriuretic peptide levels in chronic respiratory failure with cor pulmonale. Respir Med 1999; 93:507–514
105 Ando T, Ogawa K, Yamaki K, et al. Plasma concentrations of atrial, brain, and C-type natriuretic peptides and endothelin-1 in patients with chronic respiratory diseases. Chest 1996; 110:462–468
106 Ishii J, Nomura M, Ito M, et al. Plasma concentration of brain natriuretic peptide as a biochemical marker for the evaluation of right ventricular overload and mortality in chronic respiratory disease. Clin Chim Acta 2000; 301:19–30
107 Nagaya N, Sasaki N, Ando M, et al. Prostacyclin therapy before pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension. Chest 2003; 123:338–343
108 Chen S, Garami M, Gardner DG. Doxorubicin selectively inhibits brain versus atrial natriuretic peptide gene expression in cultured neonatal rat myocytes. Hypertension 1999; 34:1223–1231
109 Suzuki T, Hayashi D, Yamazaki T, et al. Elevated B-type natriuretic peptide levels after anthracycline administration. Am Heart J 1998; 136:362–363
110 Park MH, Scott RL, Uber PA, et al. Usefulness of B-type natriuretic peptide levels in predicting hemodynamic perturbations after heart transplantation despite preserved left ventricular systolic function. Am J Cardiol 2002; 90:1326–1329
111 Natrecor [package insert]. Sunnyvale, CA: Scios, 2001
112 Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure: Nesiritide Study Group. N Engl J Med 2000; 343:246–253
113 Hobbs RE, Miller LW, Bott-Silverman C, et al. Hemodynamic effects of a single intravenous injection of synthetic human brain natriuretic peptide in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 1996; 78:896–901
114 Marcus LS, Hart D, Packer M, et al. Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure: a double-blind, placebo-controlled, randomized crossover trial. Circulation 1996; 94:3184–3189
115 Mills RM, LeJemtel TH, Horton DP, et al. Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure: a randomized, double-blind, placebo-controlled clinical trial; Natrecor Study Group. J Am Coll Cardiol 1999; 34:155–162
116 The VMAC (Vasodilatation in the Management of Acute CHF) Investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA. 2002; 287:1531–1540
117 Lainchbury JG, Richards AM, Nicholls MG, et al. The effects of pathophysiological increments in brain natriuretic peptide in left ventricular systolic dysfunction. Hypertension 1997; 30:398–404
118 Okumura K, Yasue H, Fujii H, et al. Effects of brain (B-type) natriuretic peptide on coronary artery diameter and coronary hemodynamic variables in humans: comparison with effects on systemic hemodynamic variables. J Am Coll Cardiol 1995; 25:342–348
119 Yoshimura M, Yasue H, Morita E, et al. Hemodynamic, renal, and hormonal responses to brain natriuretic peptide infusion in patients with congestive heart failure. Circulation 1991; 84:1581–1588
120 Brunner-La Rocca HP, Kaye DM, Woods RL, et al. Effects of intravenous brain natriuretic peptide on regional sympathetic activity in patients with chronic heart failure as compared with healthy control subjects. J Am Coll Cardiol 2001; 37:1221–1227
121 Aronson D, Burger AJ. Intravenous nesiritide (human B-type natriuretic peptide) reduces plasma endothelin-1 levels in patients with decompensated congestive heart failure. Am J Cardiol 2002; 90:435–438
122 Levine HJ, Gaasch WH. Vasoactive drugs in chronic regurgitant lesions of the mitral and aortic valves. J Am Coll Cardiol 1996; 28:1083–1091
123 Otto CM. Evaluation and management of chronic mitral regurgitation. N Engl J Med 2001; 345:740–746
124 Burger AJ, Horton DP, LeJemtel T, et al. Effect of nesiritide (B-type natriuretic peptide) and dobutamine on ventricular arrhythmias in the treatment of patients with acutely decompensated congestive heart failure: the PRECEDENT study. Am Heart J 2002; 144:1102–1108
125 Burger AJ, Elkayam U, Neibaur MT, et al. Comparison of the occurrence of ventricular arrhythmias in patients with acutely decompensated congestive heart failure receiving dobutamine versus nesiritide therapy. Am J Cardiol 2001; 88:35–39

126 Silver MA, Horton DP, Ghali JK, et al. Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure. J Am Coll Cardiol 2002; 39:798–803
127 Stevenson LW, Massie BM, Francis GS. Optimizing therapy for complex or refractory heart failure: a management algorithm. Am Heart J 1998; 135:S293–S309
128 Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. JAMA 2002; 287:628–640
129 Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation 2002; 106:920–926