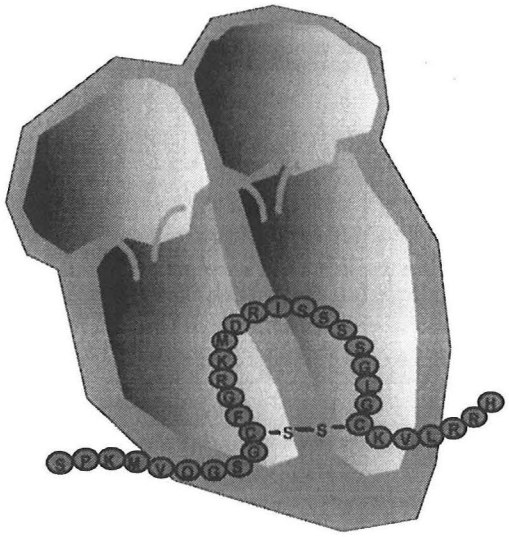
The Diagnostic and Therapeutic Uses of B-type Natriuretic Peptide (BNP) in Cardiovascular Disease



James de Lemos
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Dr. de Lemos **has not** disclosed financial or other relationships with commercial concerns related directly or indirectly to this program. Dr. de Lemos **will** be discussing off-label uses in his presentation

James de Lemos, MD
Assistant Professor of Medicine
Cardiology Division

Dr. de Lemos is the director of the CCU at Parkland Hospital and a clinical researcher with interests in the acute coronary syndromes. His research efforts have focused on measures of tissue perfusion after fibrinolytic therapy and the use of cardiac biomarkers to assess prognosis in patients with acute coronary syndromes. He is currently an Associate in the Donald W. Reynolds Cardiovascular Clinical Research Center.

Historical Perspective

In 1956 a series of experiments established the heart as an endocrine organ. First, Kisch and colleagues detected secretory granules in guinea pig atria.[1] Henry and Pearce subsequently described increased urinary flow after balloon stretch of the canine left atrium.[2] Twenty-five years later, de Bold injected homogenized atrial tissue into rats and observed increased sodium excretion and urinary volume.[3] In 1984, the structure of atrial natriuretic peptide (ANP) was identified,[4] and in 1988 a compound was identified from porcine brain that caused natriuretic and diuretic responses similar to ANP.[5] Although this peptide was called brain (B-type) natriuretic peptide (BNP), it was soon realized that the primary site of BNP synthesis was actually ventricular myocardium.[6,7] In 1990 a third member of the natriuretic peptide family was identified, also from porcine brain, and called C-type natriuretic peptide (CNP).[8] CNP is structurally distinct from ANP and BNP and is expressed to a much greater extent in CNS and vascular tissues than in the heart.[9] In 1992, a fourth member of this class was identified from the venom of the green mamba snake, *Dendroaspis angusticeps,* and called Dendroaspis natriuretic peptide (DNP).[10] DNP immunoreactivity has been identified in human plasma and atrial myocardium.[11]

Synthesis and Release of ANP and BNP

Approximately 1% of total atrial mRNA codes for ANP. Stretch of atrial myocytes leads to synthesis of a 150 amino acid precursor protein (pre-pro-ANP), which is stored in intracellular storage granules as a 126 amino acid prohormone after removal of a 24 amino acid signaling sequence during cellular transport. At the time of secretion the prohormone is cleaved into a 98 amino acid N-terminal fragment (N-proANP) and the 28 amino acid active hormone (ANP). N-proANP has a much longer half-life than ANP, which has a half-life of only 2-3 minutes. The plasma concentration of N-proANP is ~50X higher than the plasma concentration of ANP, and fluctuates much less in response to minor hemodynamic changes. As a result, laboratory measurements of N-ProANP are more reliable than those of ANP, and as will be discussed below, N-ProANP has proven to be superior to ANP as a cardiac biomarker. Furthermore, there is evidence that some N-terminal fragments have biologic activity similar to ANP.[12]

BNP gene expression occurs more rapidly in response to an appropriate stimulus than does ANP gene expression. In a rat model of acute MI, ventricular BNP gene expression occurred many hours earlier than atrial ANP expression.[13] Like ANP, BNP is stored as a pro-hormone, and secreted a 76 amino acid N-terminal fragment (N-proBNP) and a 32 amino acid active hormone (BNP). The circulating half-life of BNP is much longer than ANP due to a lower sensitivity of BNP for the natriuretic peptide clearance receptor (NPR-C).[14] The half-life of BNP and N-proBNP do not differ to the same extent as is observed with ANP and N-proANP: as a result, there is no clear rationale for selecting N-proBNP over BNP as a cardiac biomarker.

The stimulus for natriuretic peptide release is thought to be myocyte stretch, rather than pressure load.[15-17] One study has shown that pericardial tamponade, a condition that increases atrial pressure without causing atrial stretch, does not result in elevated ANP levels.[15] Another study compared BNP levels between patients with idiopathic dilated cardiomyopathy and those with hypertrophic cardiomyopathy. Patients in the two groups had similar LV end diastolic pressure and similar LV mass. BNP levels were 4 times

higher among the group with IDC. The difference in BNP between the groups correlated with differences in LV end diastolic volume,[18] further suggesting that stretch (wall stress), rather than transmural pressure, is the primary stimulus for BNP synthesis. In clinical practice, conditions that cause pressure overload of the atria or ventricles usually increase wall stress, so the distinction between transmural pressure and wall stress is generally not clinically meaningful.

Synthesis of natriuretic peptides may be modulated by vasoactive peptides such as endothelin and angiotensin II, independent of the effect of these agents on hemodynamic parameters.[16,17,19,20] ANP and BNP are differentially regulated: conditions that cause atrial but not ventricular overload result in a greater increase in ANP than BNP.[21] (see table 1). ANP levels are more closely related to left atrial pressure (and PCWP) than BNP, whereas BNP is more closely related to LV pressure and volume indices.[22] Furthermore, there is some evidence that control of BNP secretion occurs at the level of gene expression, whereas ANP regulation may occur at the level of secretion of the hormone from storage granules.[23,24] Some overlap between sites of ANP and BNP synthesis occurs under pathologic conditions: during atrial overload, BNP is expressed and released in modest amounts from atrial tissue,[25,26] and ANP is also released in small amounts from ventricular tissue in the setting of myocardial infarction or left ventricular dysfunction.[7,27]

Table 1. Differential Secretion Patterns of ANP and BNP [21]

Diagnosis	PCWP (mm Hg)	LVEDP (mm Hg)	ANP (pg/mL)	BNP (pg/mL)
Normal control	7.2 ± 1.1	6.8 ± 1.2	98 ± 41	< 10
Mitral Stenosis	16.7 ± 4.7	7.6 ± 2.0	356 ± 169	147 ± 54
Dilated cardiomyopathy	15.1 ± 7.7	16.4 ± 7.8	331 ± 323	333 ± 323

Natriuretic Peptide Binding and Clearance

Three natriuretic peptide receptors have been identified (NPR-A, -B, and -C). Binding of natriuretic peptides to the A and B receptors causes formation of the secondary messenger cyclic GMP. Cyclic GMP mediates most of the biologic effects of the natriuretic peptides. (figure 1) ANP and BNP appear to bind preferentially to NPR-A and CNP to NPR-B.[28] NPR-C is thought to function predominantly as a clearance receptor: binding of natriuretic peptides to NPR-C leads to cellular uptake and degradation of the peptide. Lower affinity of BNP for this receptor explains the prolonged half-life of BNP relative to ANP.[14] The second mechanism of natriuretic hormone inactivation is cleavage by neutral endopeptidase (NEP), a zinc metallopeptidase that is present on endothelial cells, smooth muscle cells, cardiac myocytes, renal epithelium, and fibroblasts.[29] Novel pharmacologic compounds that inhibit NEP augment circulating BNP levels, a feature that appears to have significant clinical relevance.

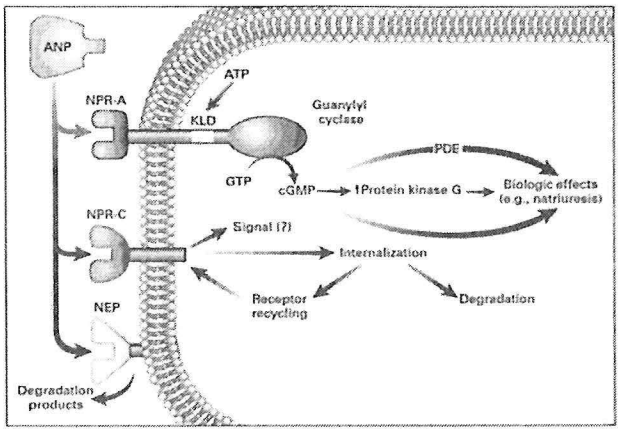

Figure 1. Binding and degradation of natriuretic peptides. From Levin et al. *N Engl J Med* 1998;339:321-8.

Actions of Natriuretic Peptides

ANP and BNP appear to have identical actions. (table 2) In the kidney, these hormones act at the glomerulus to increase glomerular filtration rate, and at the collecting duct to inhibit sodium reabsorption, causing natriuresis and diuresis.[30] In addition, the natriuretic peptides relax vascular smooth muscle, causing arterial and venous dilation and leading to a reduction in blood pressure and ventricular preload.[31] ANP and BNP also have central sympathoinhibitory effects, in part due to stimulation of vagal afferents.[32] At physiologic levels, both hormones block cardiac sympathetic nervous system activity, and at high doses, BNP blocks sympathetic activation even when cardiac filling pressures decrease.[33] These hormones also inhibit the renin-angiotensin-aldosterone axis: ANP infusion directly blocks renin and aldosterone secretion, and further inhibits the stimulatory effect of Angiotensin II on aldosterone release.[34-36] BNP appears to have direct lusitropic (relaxing) properties in the myocardium,[37] and may have antiproliferative and antifibrotic effects in vascular tissues.[38-40] In contrast to ANP and BNP, the actions of CNP are primarily limited to the vasculature, where it acts as a potent vasodilator and inhibitor of vascular cell proliferation,[41] and in the CNS, where it appears to have multiple functions.[42]

Table 2. Actions of natriuretic peptides

Renal	**Vacular**	**Cardiac**	**SNS/RAAS**
↑ GFR	↓ Arterial tone	Lusitropic	↑ Vagal tone
↑ Na^+ resorbtion	↓ Venous tone	Antifibrotic	↓ SNS activity
	Antiproliferative	Antiproliferative	↓ Renin release
			↓ Aldosterone release

SNS=sympathetic nervous system
RAAS=renin-angiotensin-aldosterone system

NATRIURETIC PEPTIDES AS CARDIAC BIOMARKERS

For a biomarker to be valuable in clinical practice, it should 1) be able to be measured rapidly and accurately 2) add diagnostic or prognostic information to currently available tools, and 3) help to guide patient management. As will be reviewed below, natriuretic peptides, and in particular BNP (and N-proBNP) fulfill most of these criteria for use in patients with suspected CHF. The plasma concentrations of ANP, N-proANP, BNP, and N-proBNP are significantly increased among patients with CHF due to LV systolic dysfunction. The concentrations of these markers increase in proportion to the severity of CHF and correlate with hemodynamic status and with LV ejection fraction. Studies comparing BNP with ANP and N-proANP suggest that BNP has a more favorable "signal to noise" ratio than ANP and N-proANP, and is also better predictive of disease state and prognosis. Furthermore, commercially available assays for BNP are now available and approved for clinical use. N-proBNP appears to provide information similar to BNP, and commercially available assays for this marker will soon be available.

Diagnosis of Congestive Heart Failure

Congestive heart failure can be a very difficult diagnosis to confirm, because the signs and symptoms are not specific. These limitations are particularly relevant when symptoms are mild or when patients have comorbid illnesses that may mimic CHF. BNP has been evaluated recently as a tool to distinguish CHF from other conditions causing dyspnea in the acute care setting. Davis et al. measured ANP and BNP prospectively in 52 consecutive elderly patients (mean age 74) presenting with acute dyspnea. The diagnosis was retrospectively determined by clinical review. The investigators determined that an admission BNP concentration $\geq$ 76 pg/mL more accurately distinguished CHF from primary lung diseases (93% sensitivity, 90% specificity) than did LVEF or ANP. Cowie et al found that BNP was more useful than ANP and N-proANP in diagnosing CHF in a primary care setting. Of 122 patients referred for presumed CHF, the diagnosis was correct in only approximately 30%, with the majority of patients having noncardiac diagnoses such as COPD and obesity. A BNP concentration $\geq$ 76 pg/mL had similar operating characteristics as was observed in the study by Davis described above (sensitivity 97%, specificity 84%, PPV 70%, NPV 98%).[43]

In 250 patients presenting to an urgent care setting with dyspnea, Dao et al performed blinded BNP measurements at the time of presentation. A final diagnosis was determined retrospectively by two cardiologists. Mean BNP concentration was 28-fold higher among patients with CHF than among those without CHF or LV dysfunction. Patients with known LV dysfunction but without an acute CHF exacerbation had BNP levels 3-4 times higher than those without CHF or LV dysfunction.[44] (figure 2)

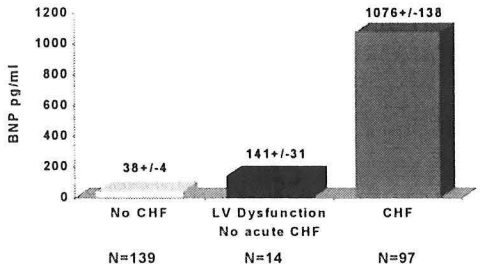

Figure 2. BNP levels in patients with CHF and asymptomatic LV dysfunction. From Dao et al. *J Am Coll Cardiol* 2001;37:379-85. Values are mean ± SEM.

Among patients with CHF exacerbations, BNP levels were highest among those with severe symptoms, intermediate among those with moderate symptoms, and lowest among those with mild symptoms. BNP also helped to distinguish which patients had edema of cardiac origin vs edema due to a noncardiac cause.[44]

Various BNP thresholds were tested in this study, and compared with clinical variables such as patient history, physical exam, x-ray, and ECG findings. (table 3)

Table 3. Comparison of BNP with other diagnostic tools in CHF[44]

Variable	Sens	Spec	PPV	NPV	Accuracy
History CHF	62	94	87	78	80
Orthopnea	47	88	74	71	72
PND	38	81	59	65	64
JVP elevated	39	94	81	69	72
Rales	56	80	66	72	70
S3	20	99	90	64	66
CXR with PVR	41	96	87	70	73
BNP > 80 pg/mL	98	92	90	98	95
BNP > 100 pg/mL	94	94	92	96	94
BNP > 120 pg/mL	90	96	95	93	94
BNP > 150 pg/mL	87	97	95	91	93

In a multivariate model including historical variables, symptoms, signs, radiologic findings, and lab findings, the addition of BNP markedly increased the explanatory power of the model, suggesting that BNP provided meaningful information not contained in the other variables.[44]

Assessment of the Severity of CHF Presentation

Among patients with dilated cardiomyopathy, the magnitude of ANP and BNP elevation correlates closely with NYHA functional class.[21,45,46] (figure 3)

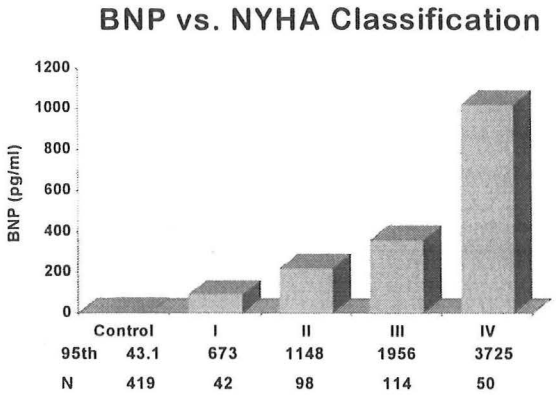

Figure 3. BNP vs NYHA classification. From Wieczorek S, *Am Heart J.* (In press)

BNP is more closely correlated with LVEF than ANP,[47,48] although patients with asymptomatic LV dysfunction may have only modest elevation in BNP. Because stretch is the primary stimulus for BNP release, individuals with compensated LV dysfunction, and low cardiac filling pressures, may have little stimulus for BNP synthesis and release. As might be expected, BNP levels correlate closely with simultaneous measurements of LVEDP and PCWP. [21,49-51] (figure 4)

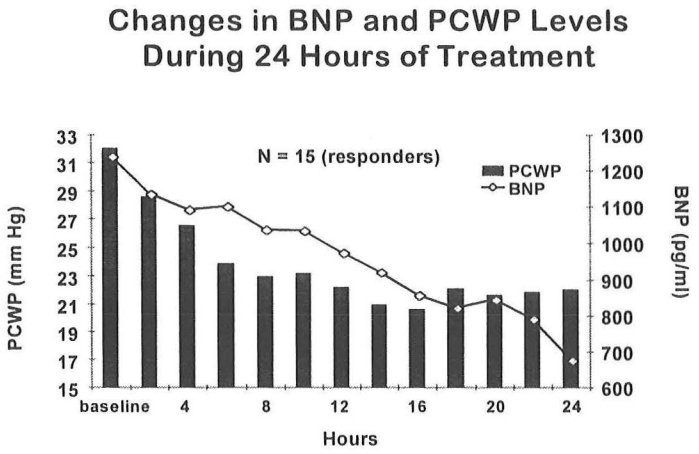

Figure 4. Correlation between PCWP and BNP. From Kazanegra et al. *J Card Fail.* 2001;7:21-9.

These pilot findings suggest that changes in BNP may be a useful noninvasive means of assessing changes in cardiac filling pressures,[50] and larger trials are currently underway to test this hypothesis.

Detection of Left Ventricular Systolic Dysfunction

A simple screening test for left ventricular dysfunction might help to identify patients at risk for developing CHF either in the general population, or in selected high-risk subsets of the population, such as those with hypertension or prior myocardial infarction. An example of the potential utility of BNP screening for asymptomatic LV dysfunction is in patients receiving anthracycline chemotherapeutic agents, where BNP levels appear to increase in advance of findings of subclinical heart failure.[52] The accuracy of BNP for the detection of *asymptomatic* LV dysfunction is lower than it is for the clinical diagnosis of heart failure, particularly when LV dysfunction is mild; BNP levels in patients with mild LV dysfunction may overlap with normal levels.[53-55] This

limitation is not unexpected in light of the close association observed between NYHA functional class and BNP.[21,45,46] BNP more accurately detects moderate or severe LV dysfunction than mild LV dysfunction.[47]

Another limitation in detecting asymptomatic LV dysfunction is confounding due to the presence of left ventricular hypertrophy (LVH). Increased LV mass is associated with elevated BNP levels, even in the presence of normal LV systolic function.[54-56] Patients with aortic stenosis and hypertrophic cardiomyopathy have elevated BNP levels even when filling pressures are normal, although the degree of elevation is less than that observed in dilated cardiomyopathy.[18,22,57] Following exercise, BNP levels rise among patients with LVH and/or LV systolic dysfunction,[58,59] and in those with ischemia,[60] but not in normal subjects. Because of a low "signal to noise" ratio in patients with asymptomatic LV dysfunction, and similar BNP levels in asymptomatic LV dysfunction and LVH, BNP screening is probably not sufficiently accurate for widespread population screening, when the goal is to identify subjects with LV systolic dysfunction[23,61] On the other hand, given the association between BNP and prognosis that will be described below, BNP screening may have a role for prognostic assessment even in unselected patient populations.

In more selected patient populations such as those with a recent myocardial infarction or those referred for echocardiography on the basis of signs or symptoms concerning for CHF, BNP appears to be a better predictor of LV dysfunction than it is in unselected populations.[48,62-64] Maisel et al evaluated BNP in a consecutive series of 200 patients referred for echocardiographic assessment of LV function. Patients with known LV dysfunction were excluded from the analyses. Mean BNP concentration was 30 pg/mL in the 53% of patients with normal LV function and 489 pg/mL in the group with abnormal LV function. A BNP threshold of 75 pg/mL had a 98% PPV and an 89% NPV for LV dysfunction. In this study, the majority of patients presented with dyspnea.[65]

Diagnosis of Diastolic Dysfunction

BNP levels are also increased among patients with diastolic dysfunction. Levels are higher among patients with systolic dysfunction than those with diastolic dysfunction, and highest among those with both systolic and diastolic dysfunction.[65] (figure 5)

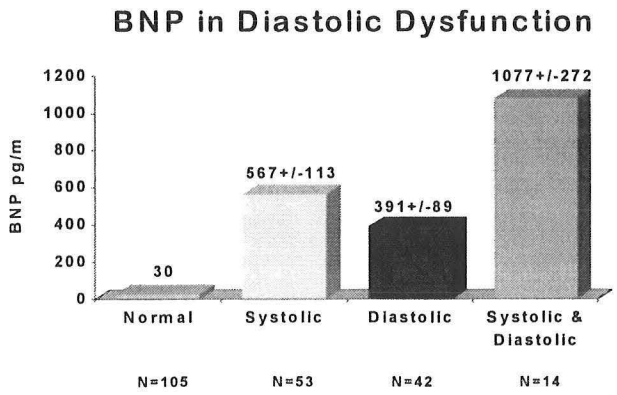

Figure 5. BNP levels in systolic and diastolic dysfunction. From Maisel et al. *Am Heart J.* 2001;141:367-74. Values are mean ± SEM.

As noted above, conditions in which diastolic dysfunction is common, such as aortic stenosis and hypertrophic cardiomyopathy, are associated with BNP elevation;[18,22,57] restrictive cardiomyopathy due to cardiac amyloidosis is also associated with marked

elevation in BNP levels.[66] Accuracy of BNP for diagnosis of isolated diastolic heart failure approaches that for diagnosis of heart failure due to systolic dysfunction.[67] Among patients with normal left ventricular function, BNP correlates with echocardiographic indices of diastolic function: BNP levels are higher than normal among patients with evidence of impaired relaxation[68] and highest among those with a restrictive filling pattern.[69] Diastolic dysfunction has proven to be a difficult disorder to study, in large part due to the absence of appropriate clinical diagnostic criteria. Incorporating BNP into diagnostic strategies may facilitate research in diastolic heart failure.

Limitations

BNP appears to be useful for the diagnosis of systolic and diastolic heart failure, and in particular appears to help distinguish cardiac dyspnea from non-cardiac dyspnea. In clinical practice, however, patients may present with dual diagnoses, such as pneumonia and heart failure, or COPD and prior LV dysfunction, and in such cases BNP may not be particularly helpful. In addition, as will be discussed below, conditions that cause right ventricular dysfunction, such as large pulmonary embolism and cor pulmonale, may result in modest elevation in BNP. While these comorbid conditions may lower the positive predictive value associated with *modest* BNP elevation, *marked* BNP elevation (> 600-800 pg/mL) maintains a high positive predictive value for CHF. In addition, the high negative predictive value should be emphasized: a normal BNP level largely excludes decompensated CHF as a diagnosis, regardless of the clinical circumstances.[70]

Summary of the Diagnostic Role of BNP testing

The first widespread clinical use of BNP will likely be to "rule out" CHF in the urgent care setting. Although there are limitations to this approach, a normal BNP in the setting of acute dyspnea makes the diagnosis of CHF unlikely. Among patients with known CHF, an increase in BNP from the patient's "baseline" suggests an exacerbation of disease. BNP is less useful for population screening in asymptomatic patients, because asymptomatic LV dysfunction is associated with only modest BNP elevation, and cannot be readily distinguished from LVH. However, in selected populations, such as patients following myocardial infarction and those receiving cardiotoxic drugs, BNP may be a sensitive screening measure for asymptomatic LV dysfunction. Finally, BNP shows promise as a tool to diagnose diastolic heart failure in the appropriate clinical setting. Elevated BNP in a patient with dyspnea and normal LVEF is suggestive of diastolic dysfunction, provided "right ventricular" causes of BNP elevation, such as pulmonary embolism and cor pulmonale, have been excluded.

Prognostic Assessment

The prognostic role of BNP has been evaluated in patients with chronic heart failure, in the stable phase following nonfatal MI, in the early phase of an acute coronary syndrome, and in the general population. In addition, data are emerging with regard to

the prognostic implications of BNP elevation in a number of other diseases such as pulmonary embolism, aortic stenosis, and primary pulmonary hypertension.

BNP for Prognostic Assessment in Chronic Heart Failure

Among patients with chronic heart failure, higher levels of BNP are associated with increased cardiovascular and all-cause mortality, independent of age, NYHA class, prior MI, and LVEF.[71-73] In mulitivariate analyses, BNP is a more powerful predictor of mortality than is NYHA class or LVEF,[71-73] and in one study of outpatients with chronic CHF, plasma neurohormone levels were more predictive of death or the need for cardiac transplantation than was maximal $V0_2$ measured during cardiopulmonary exercise testing.[74] In addition to predicting mortality, elevated BNP predicts the need for heart failure readmission.[75] Recent studies also suggest that BNP provides similar prognostic information in diastolic heart failure as it does in systolic heart failure.[76]

While a single (baseline) BNP provides important prognostic information, serial BNP testing may be of even greater value. BNP measurements performed $\geq$ 3 months after initiation of CHF therapy provide even greater prognostic value than do baseline measurements.[72,73] In a pilot study of 72 patients hospitalized with decompensated CHF, mean BNP levels increased during the hospital stay among patients who died or were readmitted within the 30-day followup period, while mean BNP levels decreased among patients who did not develop a clinical endpoint.[77] In this study, admission BNP, discharge BNP, and the change in BNP were all predictive of mortality.[77]

BNP Following Transmural MI

Initial studies evaluating the prognostic implications of neurohormonal activation after ST elevation MI (AMI) focused on ANP and N-proANP. While these studies demonstrated that both markers were predictive of adverse outcomes, N-proANP performed better than ANP for this purpose.[78-81] However, after adjustment for LVEF, the prognostic value of ANP and N-proANP was limited.[23,82] BNP has been shown to be a superior prognostic marker to ANP and N-proANP in patients with AMI.[23,83-85] ANP release appears to be less predictable than BNP release after AMI. In some patients with AMI, ANP levels are maximal at presentation, and then decrease thereafter,[86,87] further supporting the notion that ANP is released rapidly from storage granules under conditions of increased atrial stretch, whereas BNP levels more closely mirror changes in gene expression. BNP levels rise many-fold higher than ANP levels in the early phases of AMI (and > 10X normal), thus increasing the signal-to-noise ratio of BNP relative to ANP and N-proANP.[84,86,87] Omland et al found that ANP, N-pro-ANP, and BNP were all univariate predictors of cardiovascular death in survivors of AMI, but in multivariate analyses, only BNP provided prognostic information independent of LVEF.[23]

BNP concentration rises rapidly over the first 24 hours after myocardial infarction and then tends to stabilize; patients with a large infarct may have a second peak approximately 5 days later.[86,88,89] When measured between 1 and 7 days after the onset of AMI, BNP identifies patients at risk for adverse left ventricular remodeling,[90] left ventricular dysfunction,[84,87,89,90] clinical congestive heart failure,[84] and death.[23,83-85] As is observed in chronic heart failure, the prognostic power of BNP following AMI appears

to be greater than LVEF.[23,83,84] In addition, the predictive value is independent of age and prior history of CHF.[23,83,84]

BNP in Acute Coronary Syndromes

The studies described above were small case-control studies, limited to patients with ST elevation MI. The prognostic value of BNP in patients with unstable angina and non-ST elevation MI has only recently been evaluated. In two cross-sectional studies, levels of BNP were higher among patients with unstable angina than those with stable angina or among healthy controls.[91,92] Elevated BNP correlated better with regional wall motion abnormalities than with hemodynamic data, and as wall-motion abnormalities improved with therapy, BNP levels fell significantly.[91]

In a small case-control study of patients with non-ST elevation ACS, N-proBNP levels were higher among patients who died than those who survived.[93] Subsequently, the prognostic value of BNP (measured a median of 40 hours after symptom onset) was evaluated in 2525 patients with acute coronary syndromes enrolled in the OPUS-TIMI 16 Study. This study included 825 patients with ST elevation MI, 565 patients with non-ST elevation MI, and 1133 with unstable angina. Higher baseline BNP levels were associated with older age, female sex, and a history of hypertension, CHF, vascular disease, and renal insufficiency. Patients with higher BNP were more likely to present in Killip Class > 1 and have ST changes on the baseline ECG and elevation in cardiac markers. BNP also correlated with the extent of coronary disease measured at the time of angiography. Although statistically significant, the correlation between BNP and LVEF was modest (table 3).[94]

Both mortality and congestive heart failure increased with higher baseline levels of BNP. This relationship was observed among patients with ST elevation MI, non-ST elevation MI, and unstable angina.[94]

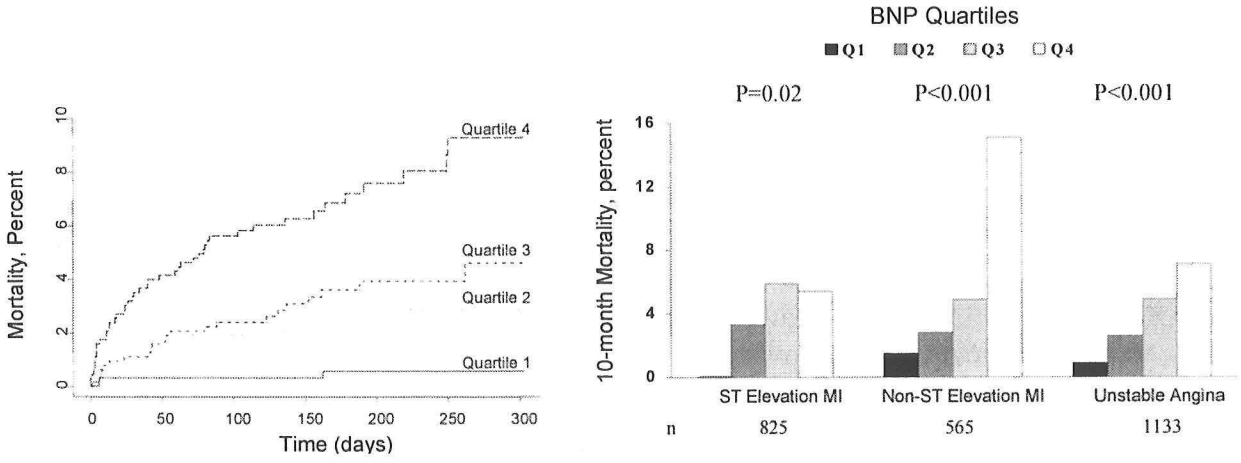

Figure 6. BNP in Acute Coronary Syndromes. From de Lemos et al. *N Engl J Med* 2001;345:1014-21.

BNP was predictive of mortality both among patients with normal and those with elevated troponin levels as well as both those with and without evidence for heart failure at presentation. After adjustment for independent predictors of mortality including age, renal function, CHF, ST deviation, and troponin I, increasing BNP concentration remained associated with higher 10-month mortality. The adjusted odds ratios in the

second, third, and fourth quartiles of BNP were 3.8 (1.1-13.3), 4.0 (1.2-13.7), and 5.8 (1.7-19.7), respectively.[94]

The explanation for the predictive value of BNP in unstable angina is not entirely clear. Unlike other biomarkers used for risk-stratification in ACS, such as troponin, CKMB, and CRP, BNP is a counterregulatory hormone that may play a role in the response to ischemic injury. In this setting, BNP may serve as an index of the size or severity of the ischemic insult, even when myocardial necrosis has not occurred. Several observations support this hypothesis. First, in experimental acute MI, BNP synthesis is augmented not only in infarcted tissue, but also in non-infarcted tissue.[13] Second, BNP rises rapidly and transiently after exercise in patients with stable CAD;[95] the level of BNP rise correlates with the size of ischemic territory by SPECT imaging.[60] Finally, BNP levels have been shown to increase transiently after uncomplicated PTCA, even when PCWP remains unchanged.[96,97] In aggregate, these findings suggest that transient ischemia increases wall stress and induces BNP synthesis and release in proportion to the degree of ischemic insult.

A recent study in animals suggests an alternative hypothesis. Mice genetically engineered to remove the natriuretic peptide receptor (GC-A) surprisingly had smaller infarct size than wild type mice after ischemia and reperfusion. Endothelial activation and tissue inflammation were also lower in the GC-A null mice. Additional studies suggested that ANP directly induced upregulation of endothelial p-selectin and activation of NF-κB. The authors speculate that high levels of natriuretic peptides may exacerbate "reperfusion injury," but the clinical implications of these findings are as yet unclear.[98]

BNP in "Right Ventricular" Processes

In primary pulmonary hypertension, BNP levels increase in proportion to the degree of RV dysfunction.[99] In one study, BNP levels above the median were associated with increased mortality over the 24 month follow-up period, independent of clinical and hemodynamic variables, including mean PA pressure and cardiac output. Mean BNP levels fell among patients who survived, but increased among those who subsequently died. BNP levels measured after 3 months of vasodilator therapy were of even greater prognostic value than were baseline values.[100] (figure 7)

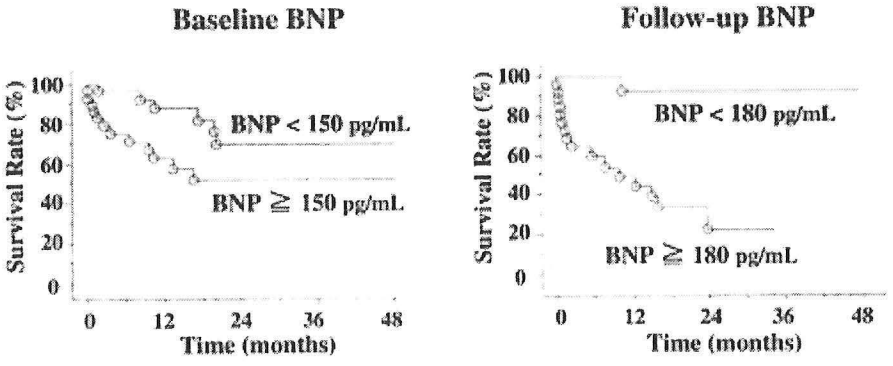

Figure 7. Prognostic role of BNP in Primary Pulmonary Hypertension. From Nagaya et al. *Circulation.* 2000;102: 865-70.

BNP is also modestly elevated in patients with cor pulmonale[101] and higher BNP levels identify patients with this disorder who are at increased risk for cardiopulmonary mortality.[102] Further evidence for the role of BNP in RV disorders comes from a study

of patients with arrhythmogenic right ventricular dysplasia (ARVD). In one small study, BNP levels were 8-fold higher among patients with ARVD than among controls or patients with right ventricular outflow tract (RVOT) tachycardia. This is clinically relevant in that clinicians often have difficulty distinguishing RVOT tachycardia from ARVD. The degree of BNP elevation in ARVD reflects the magnitude of RV dysfunction as well as the severity of the arrhythmic substrate.[103]

BNP in population-based samples

Several studies have extended the potential role of BNP measurement to population screening. In a longitudinal study of 541 elderly patients (age at entry 85 years) from Göteborg, Sweden, BNP levels predicted 5-year mortality both among patients with and those without known cardiovascular disease.[104] LV function and BNP were also measured in 1242 patients from the Glasgow MONICA survey. Mortality increased in a stepwise fashion with both decreasing LVEF and increasing BNP. Among patients with LV dysfunction, mortality at 4 years was three-fold higher among patients who had a BNP > 17.9 pg/mL (a threshold 4-fold lower than has been used in prognostic assessment of patients with CHF or CAD).[105] (figure 8)

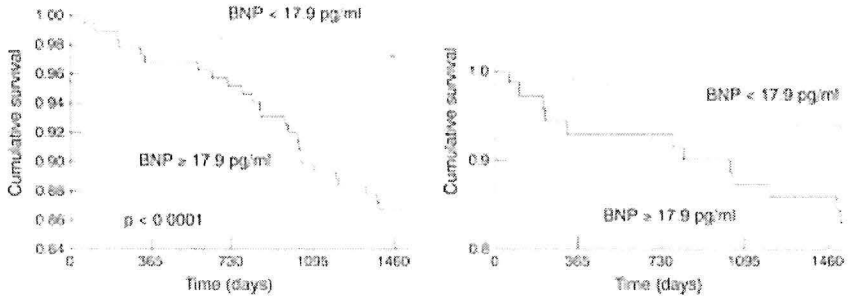

Figure 8. BNP in Population Screening. From McDonagh et al. *Heart*. 2001;86:21-6.

How should we use BNP levels to guide clinical decision-making?

Therapies for Patients with BNP elevation

ACE inhibitors and beta blockers have become routine therapy for patients with congestive heart failure due to systolic dysfunction, based on clear evidence of mortality reduction. Because each of these agents works, at least in part, to antagonize neurohormonal systems, it is possible that their effect may be greatest among patients with neurohormonal activation, as reflected by an elevated plasma concentration of BNP. One mechanism of evaluating therapies that might be of particular benefit in patients with elevated BNP is to stratify results from randomized clinical trials based on the level of BNP at enrollment. In a randomized comparison of carvedilol vs placebo in 415 patients with chronic ischemic heart failure, a BNP level above the median (~82 pg/mL) was independently associated with death and progression of CHF. Treatment with carvedilol significantly reduced mortality and progression of heart failure among patients with BNP levels above the median, but not those with BNP below the median.[71] On the otherhand, in a subgroup analysis from the SAVE trial involving 534 patients, captopril therapy did

not result in greater benefit among patients with N-proANP elevation (BNP was not measured).[106] These studies are far from conclusive, and additional large studies are clearly needed to identify which therapies are most beneficial among patients with BNP elevation. Given the interest in BNP testing, it is likely that most future CHF trials will meaure BNP and stratify either randomization or trial results based on BNP levels.

Several small studies have performed serial measurements of BNP, before and after initiation of therapy, to determine the effect of a particular pharmacologic agent on neurohormonal activation. These studies have not been large enough to evaluate outcome data, and thus cannot link BNP lowering with a reduction in clinical endpoints. ACE inhibitor therapy results in early and sustained reduction in natriuretic peptide levels:[48,107,108] this effect is dose-dependent,[109,110] which may help to explain the clinical benefit of high- vs low-dose ACE inhibition in patients with chronic CHF.[111] In addition, following myocardial infarction, ACE inhibitors may prevent the second peak in BNP that occurs as the ventricular remodeling process begins.[112] The addition of spironolactone to conventional therapy has been shown to further reduce BNP levels. The reduction in BNP observed with spironolactone correlated with favorable changes in left ventricular remodeling.[113]

The effects of beta-blockers on natriuretic peptides are more complex. An antagonistic relationship exists between the beta-adrenergic and natriuretic peptide systems. As discussed above, natriuretic peptides inhibit sympathetic activity. In experimental models, adrenergic stimulation inhibits ANP release,[114] and in population studies therapy with beta-blockers increases BNP levels.[115] In contrast, among patients with idiopathic dilated cardiomyopathy, the addition of carvedilol to conventional therapy with ACE inhibitors *reduced* BNP levels over 6-months followup. The reduction in BNP paralleled improvements in LV dimensions and function.[116] The discrepant findings between population studies and studies of patients with CHF can be explained by the differences in patient populations. Among patients with CHF, the reduction in BNP reflects improvement in hemodynamic parameters and LV function, which overcomes the intrinsic BNP-raising effects of beta-blockade.

Tailoring therapy to BNP levels in CHF

As a noninvasive marker that correlates closely with filling pressures in patients with symptomatic CHF, BNP might be useful as a target for therapy. Unfortunately, few data are available in which BNP levels have been used to guide clinical decisions. Troughton and colleagues randomized 69 patients with CHF to either symptom-guided therapy or therapy titrated to the level of N-proBNP. The group assigned to N-proBNP titration received higher doses of ACE inhibitors and diuretics than patients treated traditionally, and also were more likely to receive spironolactone. After approximately 10 months of followup, fewer events occurred in the group treated based on N-proBNP levels than the group treated using traditional indices.[117] As Dries and Stevenson note in an accompanying editorial, titrating therapy to BNP was not straightforward, as there was significant intra- and inter-individual variability.[118] In another small randomized study of 20 patients, the group in whom ACE inhibitor dose was titrated to BNP levels had greater reduction in BNP and heart rate than the group managed with empiric therapy. However, hemodynamic measurements improved to a similar degree in both groups.[110]

BNP for clinical decision-making in acute coronary syndromes

Therapy for patients who present with BNP elevation in the setting of ACS has not been defined. BNP was measured in a substudy of the TACTICS study, which compared invasive vs conservative strategies for patients with non-ST elevation ACS. As expected, subjects with an elevated BNP (> 80 pg/mL) were at increased risk for mortality, independent of other predictive variables. However, an early invasive strategy did not reduce mortality among patients with BNP elevation, and there was no interaction between BNP elevation and the observed benefit of invasive therapy in reducing nonfatal ischemic endpoints.(unpublished data) These observations highlight the chief limitation of BNP testing in ACS: although a high-risk group can be identified, it is not clear how these patients should be managed differently. On the other hand, the identification of a *low-risk* group may be of immediate benefit, as these patients may avoid costly and risky therapies that are unlikely to benefit them.

Summary of the Role of BNP for Assessing Prognosis

BNP is useful for predicting the risk for death and CHF in a wide variety of patients, including those with chronic heart failure, those recovering from MI, and more recently, patients with ACS who do not have evidence of myocardial necrosis. Further, preliminary evidence suggests that BNP may even be useful for risk-stratification in the general population. The predictive value of BNP is independent of clinical variables, the severity of heart failure, and LVEF. Reassessing BNP after the initiation of therapy appears to augment the prognostic value, to help assess the response to treatment, and possibly to guide therapeutic titration. Patients who have no reduction in BNP levels despite aggressive therapy for CHF are at particularly high risk for adverse outcomes. The major limitation in the use of BNP testing is that the management implications are not clear: while patients at high risk can be clearly identified, specific therapies for patients with BNP elevation have not been defined.

At the present time, it appears reasonable to treat patients with BNP elevation in the setting of CHF intensively with established therapies such as beta-blockers, ACE inhibitors, and spironolactone. Whether elevated BNP in the absence of signs or symptoms of volume overload should lead to an increase in diuretic dose is not known. For patients with BNP elevation following ACS, future studies are needed before therapeutic recommendations can be made.

BNP AS A THERAPUETIC AGENT

Given the beneficial physiologic actions of BNP, including natriuresis, balanced vasodilation, inhibition of the sympathetic nervous system, and antagonism of the renin-angiotensin-aldosterone axis, the development of BNP as a therapeutic agent appears logical. When recombinant BNP (nesiritide) was approved for clinical use by the FDA earlier this year, it represented the first new parenteral drug approved for the treatment of decompensated congestive heart failure since milrinone was approved over 10 years ago. The FDA approval of nesiritide was based on demonstration of hemodynamic benefits and safety rather than clinical event reduction.

Initial small phase II studies with nesiritide showed dose-dependent improvement in hemodynamic abnormalities in patients with severe (class III-IV) CHF. At the highest dosages evaluated, nesiritide decreased PCWP by ~ 50%, improved cardiac index by ~ 25%, and improved urinary flow rate by about 25%.[119-121] Blood pressure dropped by an average of 10 mm Hg, with larger reductions observed in some patients. Abraham and colleagues infused nesiritide at either 0.025 or 0.05 μg/kg/min or placebo for 4 hours in 16 patients with decompensated CHF. In an attempt to separate the diuretic effects from the hemodynamic effects of this agent, the investigators replaced urine volume on an hourly basis. Nesiritide decreased PCWP by 40% and increased cardiac output by 28% despite overall neutral fluid balance. In addition, nesiritide reduced norepinepherine and aldosterone levels.[122] In another small study (n=29) a 24-hour infusion of nesiritide was evaluated. Hemodynamic benefits of nesiritide were observed within the first hour of therapy (PCWP decreased by 28% in the highest dose arm). Peak hemodynamic effects were seen at 3-6 hours and the effect was maintained through the 24-hour infusion period. Several patients required dose-reduction due to hypotension.[123]

Phase "3" Studies of Nesiritide

Colucci et al simultaneously reported results from two randomized trials in 2000,[124] a 127 patient double-blind placebo-controlled efficacy trial and a 305 patient open-label trial comparing nesiritide with "standard therapy." In the placebo-controlled efficacy trial, a six-hour infusion of either 0.015 or 0.030 μg/kg/min nesiritide significantly improved hemodynamic parameters (table 4). In addition, global clinical status, as assessed both by the patient and the provider, was significantly improved.

Table 4. Change in hemodynamic status at six hours[124]

Variable	Placebo	Low-dose Nesiritide	High-dose Nesiritide	P Value
PCWP (mm Hg)	+ 2.0 ± 7.2	- 6.0 ± 7.2	- 9.6 ± 6.2	<0.001
Right atrial pressure	+ 0.4 ± 4.6	- 2.6 ± 4.4	- 5.1 ± 4.7	<0.001
CI (l/min/m2)	- 0.1 ± 0.5	+ 0.2 ± 0.5	+ 0.4 ± 0.7	<0.001
SBP	+ 0.3 ± 11	- 4.4 ± 10.2	- 9.3 ± 12.6	0.001
Mean PAP	+ 2.0 ± 5.9	-7.0 ± 6.9	- 7.7 ± 7.6	<0.001
PVR	+ 26 ± 197	- 62 ± 100	- 2 ± 142	0.03
Heart rate	+ 1.4 ± 7.5	- 1.6 ± 7.1	+ 0.0 ± 8.8	0.22

In the open-label trial, invasive hemodynamic monitoring was not performed routinely. The two doses of nesiritide were compared with "standard therapy," which consisted of a single intravenous agent used for treatment of CHF, either dobutamine (57%), milrinone (19%), nitroglycerin (18%), dopamine (6%), or amrinone (1%). Nesiritide and standard therapy resulted in similar improvements in global clinical status, dyspnea, and fatigue. In the nesiritide arms, symptomatic hypotension was observed more frequently: 4% in standard therapy arm, 11% in low-dose nesiritide arm, and 17% in the high dose arm ($p=0.008$). Sustained VT was rare in all groups. Nonsustained VT occurred in 8 % of patients in the standard therapy arm, 10% in the low-dose nesiritide arm, and 1% in the high-dose arm ($p<0.02$).[124] The initial new drug application for nesiritide was not approved by the FDA, primarily because of reservations about safety.

One of the unique properties of BNP is its ability to lower filling pressures and increase cardiac output without causing tachycardia. This is a function of the sympathoinhibitory effects described above. Studies to date have found either no effect or only minor increase in heart rate in patients treated with nesiritide. In addition, in a prospective randomized trial (PRECEDENT) nesiritide was associated with a significantly lower risk for ventricular arrhythmias and cardiac arrest than was dobutamine (mean dose of dobutamine ~ 5 μg/kg/min).[125]

The Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial compared nesiritide with placebo or nitroglycerin in 498 patients with acute decompensated CHF. The dose of nesiritide used in VMAC was significantly lower than that used in the Colucci trials. Patients receiving PA catheters were randomized separately from those managed without PA catheters. The study design was complex. For patients with PA catheters, initial randomization was to placebo, fixed-dose nesiritide (2.0 μg/kg bolus, followed by 0.01 μg/kg/min infusion) or adjustable-dose nesiritide (at three hours, option to give another 1.0 μg/kg bolus and gradually increase infusion to a maximum 0.03 μg/kg/min). After a 3-hour period, the placebo-treated patients were switched to either nitroglycerin or fixed-dose nesiritide. The primary endpoint was change in PCWP. For patients managed without a PA catheter, there was no adjustable-dose nesiritide arm. The primary endpoint in patients without a PA catheter was dyspnea score. Background therapy could include standard CHF therapies such as dobutamine.[126]

Nesiritide lowered PCWP significantly more than nitroglycerin at 3 and 24 hours. Nesiritide improved dyspnea vs placebo but not when compared with nitroglycerin. The most common adverse effect of nesiritide was headache, which occurred in 8% in the nesiritide-treated patients and 20% in patients receiving nitroglycerin. With the lower dose of nesiritide used in VMAC, symptomatic hypotension occurred in 5% of patients in both the nesiritide and nitroglycerin groups.[126]

These data were initially presented in November 2000, but have yet to be published. On the basis of the additional data from the PRECEDENT and VMAC trials, the FDA has approved nesiritide for clinical use. Despite its approval, the role of nesiritide in clinical practice has yet to be clearly defined. Of concern, only surrogate endpoints have been evaluated to date. In addition, studies comparing nesiritide with "best available" therapy have not been performed.

Vaspeptidase Inhibitors

As described above, ANP and BNP clearance involves two mechanisms: binding to the clearance (NPR-C) receptor and degradation by neutral endopeptidase (NEP). In addition to degrading natriuretic peptides, NEP catalyses degradation of the vasodilators bradykinin and adrenomedullin, and the vasoconstrictors endothelin-1 and angiotensin II.[127] In animals with experimental CHF, there is evidence for upregulation of NEP.[128] Selective NEP inhibitors may cause either vasodilation or vasoconstriction, depending on whether vasodilator or vasoconstrictor substrates are preferentially effected.

The unpredictable effects of NEP inhibition on vascular tone are largely overcome by combining ACE and NEP inhibition: greater hemodynamic and renal effects are observed with combined inhibition vs selective inhibition.[127] Omipatrilat is compound in late clinical development that inhibits both NEP and ACE. The initial development of this compound focused on hypertension. When compared with other antihypertensive agents, omipatrilat appears to result in greater blood pressure lowering, particularly with respect to systolic blood pressure. The effect on systolic blood pressure suggests favorable effects on large artery compliance.[127] The initial new drug application for omipatrilat was denied by the FDA due to concerns about an increased incidence of angioedema, particularly at higher dosages.[129] Angioedema is thought to be caused by increased circulating levels of bradykinin, which is inactivated by both ACE and NEP. The OCTAVE (Omipatrilat Cardiovascular Treatment Assessment Versus Enalapril) trial is evaluating the incidence of angioedema in 25,000 patients with poorly controlled hypertension.

In animal models of CHF, short-term treatment with omipatrilat improves ventricular function, promotes natriuresis, and decreases cardiac filling pressures and peripheral vascular resistance; long-term therapy improves ventricular geometry and survival vs captopril.[130-132] The cardiorenal effects of omipatrilat are attenuated by antagonists of natriuretic peptide receptors, demonstrating that augmentation of the cardiac natriuretic peptide system is responsible for many of the beneficial effects of this drug.[132]

In a dose-ranging study in humans with CHF, omipatrilat caused dose-dependent reductions in blood pressure and PCWP, and an improvement in cardiac output.[133] McClean and colleagues demonstrated that 3 months of therapy with omipatrilat improved LVEF and functional status, caused natriuresis, and resulted in significant blood pressure and heart rate lowering in patients with NYHA class III-IV CHF. Omipatrilat causes an increase in post-dose ANP and cyclic GMP levels but a reduction in pre-dose BNP and norepinepherine levels.[134] The reduced BNP levels after long-term therapy are thought to reflect an improvement in hemodynamic status. The IMPRESS (Inhibition of metalloproteinase in a Randomized Exercise and Symptoms Study in Heart Failure) study randomized 573 patients with NYHA class II-IV CHF to treatment with omipatrilat (40 mg/day) or lisinopril (20 mg/day) for 12 weeks.[135] There was no difference in the primary endpoint (improvement in exercise duration), but patients randomized to omipatrilat had a lower incidence of the composite endpoint of death, rehospitalization, or discontinuation of study therapy for worsening heart failure (RR 0.52, 95% CI 0.28-0.96). In addition, creatine elevation was less common with omipatrilat than lisinopril. Finally ANP levels were higher and norepinepherine levels

lower with omipatrilat.[135] Larger trials evaluating omipatrilat in CHF are underway, and a number of related compounds are in various stages of development.

CONCLUSIONS

As a diagnostic test, BNP will be useful in determining which patients presenting with dyspnea in the acute care setting have CHF as the primary diagnosis. BNP is also helpful in identifying patients with asymptomatic LV dysfunction, but is less accurate for this purpose. The level of BNP rises in proportion to the severity of CHF, and BNP provides prognostic information that is independent of the LVEF, both among patients with chronic CHF and those who have survived a myocardial infarction. BNP is also an independent predictor of adverse outcomes in patients with unstable angina and non-ST elevation MI. The level of BNP after treatment is also predictive of outcomes, but it is not yet clear that BNP can serve as a titratable target for therapy. Furthermore, therapies of specific benefit to patients with elevated BNP have not been defined. Finally, BNP shows promise as a therapeutic agent: intravenous infusion of BNP (nesiritide) improves hemodynamic abnormalities but data are not available with respect to hard outcomes. A more intriguing class of agents for chronic therapy are vasopeptidase inhibitors, agents that inhibit both angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP). These agents increase circulating levels of ANP and BNP and may be beneficial in the chronic treatment of CHF. Paradoxically, these agents might prove to be of greatest benefit among patients with the highest plasma levels of BNP.

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