Consensus Panel

BNP Consensus Panel 2004: A Clinical Approach for the Diagnostic, Prognostic, Screening, Treatment Monitoring, and Therapeutic Roles of Natriuretic Peptides in Cardiovascular Diseases

Marc A. Silver, MD, Chairman; Alan Maisel, MD
Clyde W. Yancy, MD; Peter A. McCullough, MD, MPH
John C. Burnett, Jr., MD; Gary S. Francis, MD
Mandeep R. Mehra, MD; William Franklin Peacock IV, MD
Gregg Fonarow, MD; W. Brian Gibler, MD
David A. Morrow, MD; Judd Hollander, MD
Congestive Heart Failure

BNP Consensus Panel 2004: A Clinical Approach for the Diagnostic, Prognostic, Screening, Treatment Monitoring, and Therapeutic Roles of Natriuretic Peptides in Cardiovascular Diseases

Subject Index

Preface 1
Introduction and Background 2
- Background on HF and Need for Better Ways to Evaluate 3
- Biology and Physiology of Natriuretic Peptides 3
- Biosynthesis and Secretion of BNP 4
- Analytical and Assay Characteristics 4
- Physiologic Action of BNP and ANP 4
- Biologic Determinants of BNP Measurements 5
- BNP Assays 5
- Differences Between NT-proBNP and BNP 6
Diagnosis 7
- BNP Testing and the Diagnosis of Symptomatic HF 7
- Using BNP Levels to Help Triage Patients Presenting to the ED With HF 8
- Comorbidities and Special Issues Which Influence the Interpretation of BNP Levels 9
Prognosis 12
- BNP in Prognostication and Risk Stratification in Outpatients With HF 12
- BNP Levels and Prognosis in Hospitalized Patients 13
- BNP and the Prediction of Sudden Cardiac Death 14
- Association of BNP With Cardiac Troponin I in HF 14
- Natriuretic Peptide Hormone Measurement in ACS/CAD 15
Screening 15
- Screening for Ventricular Dysfunction: The Use of BNP 15
- Screening in the Higher-Risk Populations 16
Treatment Monitoring 17
- BNP Levels in the Hospitalized Patient 17
- Does High BNP Always Mean High Filling Pressure? 17
- Compensated and Decompensated BNP Levels 18
- Pitfalls and Caveats in BNP Interpretations 18
- How Often Should One Obtain a BNP Level in the Hospital? 18
- What if a BNP Level Does Not Fall During Hospitalization? 18
- BNP and Heart Transplantation 19
Therapy/Administration as a Therapeutic Agent 19
- B-Type Natriuretic Peptide as a Therapeutic Agent for Decompensated HF 19
- Current Therapies for ADHF 20
- Natriuretic Peptides as Therapy for ADHF 22
- Reverse Remodeling Effects of Natriuretic Peptides 23
- Therapeutic Summary 25
Additional Considerations 25
- Implications of BNP Levels in the Outpatient Management of HF 25
- Integrating BNP Levels Into a Rational Use of Nesiritide 26
- Toward the Future: Monitoring BNP Levels Post-Hospitalization—Implications for BNP-Guided Outpatient Treatment 26
- Toward Earlier Attention to Rising BNP Levels—Evaluations of Outpatient Nesiritide Infusions 27
Conclusions 27

Supported through unrestricted educational grants from:
Abbott Laboratories Diagnostic Division, Bayer HealthCare Diagnostic Division, Beckman Coulter, Biosite, and SCIOS
Among the most exciting developments in the field of heart failure in recent times has been the rediscovery of the natriuretic peptide system and its pleuripotent effects on cardiac structure and function. This is particularly true of its natriuretic and hemodynamic effects. There has been an explosion of the knowledge base seeking to understand the wide range of homeostatic, regulatory, and counter-regulatory functions in which the natriuretic peptide system participates. Additional interest has been stimulated by advances in technology such as point-of-care and core laboratory BNP assays and the use of the recombinant B-type natriuretic peptide nesiritide as a treatment option. Despite this recent interest, the available literature lacks a comprehensive expert review of the current science and roles of natriuretic peptides for diagnostic, prognostic, screening, treatment monitoring, and therapeutic purposes. More importantly, a summary updating and guiding the clinician on most of these advances was lacking. An expert Consensus Panel with basic, methodological, and clinical expertise was convened to summarize current knowledge in these areas and the findings and consensus statements are contained herein.

Marc A. Silver, MD; Alan Maisel, MD; Clyde W. Yancy, MD; Peter A. McCullough, MD, MPH; John C. Burnett, Jr., MD; Gary S. Francis, MD; Mandeep R. Mehra, MD; William Franklin Peacock IV, MD; Gregg Fonarow, MD; W. Brian Gibler, MD; David A. Morrow, MD; Judd Hollander, MD

From the Department of Medicine and Heart Failure Institute, Advocate Christ Medical Center, Oak Lawn, IL; University of California, San Diego, San Diego, CA; Department of Internal Medicine/Cardiology, UT Southwestern Medical Center, Dallas, TX; Division of Nutrition and Preventive Medicine, William Beaumont Hospital, Royal Oak, MI; Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN; Cleveland Clinic Foundation, Cleveland, OH; Cardiomyopathy and Heart Transplantation Center, Ochsner Clinic Foundation, New Orleans, LA; Ahmanson-UCLA Cardiomyopathy Center, Los Angeles, CA; Department of Emergency Medicine, University Hospital, Cincinnati, OH; Brigham & Women’s Hospital, Boston, MA; Department of Emergency Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA

Address for correspondence: Marc A. Silver, MD, Chairman and Clinical Professor, Department of Medicine and Heart Failure Institute, Advocate Christ Medical Center, 4440 West 95th Street, Suite 319 South, Oak Lawn, IL 60453-2600

E-mail: marc.silver@advocatehealth.com
The BNP Consensus Panel 2004

Introduction and Background

Since its approval by the United States Food and Drug Administration (FDA) in November 2000, the interest in clinical and research applications in BNP testing in the United States and around the world has been staggering. In the United States alone, it is estimated that up to 70% of all hospitals utilize BNP testing. Indeed, understanding the role and nature of the natriuretic peptide system in health and disease is occupying the minds of clinicians and investigators alike. Initially focused on the emergent, bedside diagnosis of HF, subsequent research has supported the value of testing BNP in settings outside of the emergency department (ED). Not only is it a useful adjunct to diagnosis and monitor patients with HF but recent studies now suggest that BNP provides independent prognostic information predicting risk of rehospitalization and mortality. In addition, BNP might have a role in screening high-risk patients for the presence of underlying cardiac dysfunction.

The popularity of any new test has a potential downside—too many tests may be ordered for less than appropriate reasons. Physicians have voiced concern over how best to integrate BNP testing in the clinical arena so that they can make informed decisions in diagnosing and managing patients. Extrapolation of peer-reviewed literature is sometimes needed, and it is here that clinical acumen plays a part. The statements presented in this manuscript are done so by a consensus that was structured on evidence-based medicine intermingled with clinical judgment; the authors having all used BNP testing in their practice. It should be made clear at the outset that BNP is not a stand-alone test. It is always of greatest value when it complements the physician’s clinical skills along with other available testing.

It is with these issues in mind that this BNP Consensus Panel 2004 was formed. Similar to the typical guideline recommendation process where recommendations are based predominantly on the availability of clinical outcome trials and expert opinion, this process includes all pertinent available trial data as well as expert consensus. The distinct purposes are to:

- Provide consensus statements for the clinician or health care service planner for consideration of incorporating BNP into clinical use or into a biomarker panel.

Marc A. Silver, MD, Chairman
BNP Consensus Panel 2004
• Provide an up-to-date distillation of the current and proposed application of BNP as a biomarker and therapeutic agent. Areas of specific discussion will center around:
  • Diagnosis;
  • Prognosis;
  • Screening;
  • Treatment monitoring; and
  • Therapy/administration as a therapeutic agent (Figure 1).
• Provide an overview of BNP's in their diagnostic and therapeutic role and possibly stimulate further research with this important biomarker.

This paper integrates evidence-based outcome data with expert opinion in providing recommendations for clinical use of BNP. We hope that the document will stimulate the continued investigation of the natriuretic peptide system, exploring its potential to facilitate earlier detection and prevention of disease.

**Background on HF and Need for Better Ways to Evaluate.** Over the past 100 years, cardiovascular disease (CVD) has become a leading cause of morbidity and mortality worldwide. At the beginning of the last century, CVD accounted for <10% of all deaths worldwide. With decreasing mortality from infectious diseases and accidents, there has been a substantial increase in CVD risk factors, such as obesity and diabetes. Additionally, the use of disease-modifying agents like angiotensin-converting enzyme inhibitors and β-blockers that improve survival rate after acute myocardial infarction (MI) and subsequent development of HF has increased. At the beginning of the 21st century, CVD now accounts for nearly one half of all deaths in the developed world and 25% in the developing world. By 2020, CVD is projected to be the cause of 25 million deaths each year and will surpass infectious disease as the world's leading cause of death and disability.

Figure 2 shows the increasing incidence and prevalence of HF in the United States according to the Centers for Disease Control and Prevention. In the United States alone, about 950,000 people die of CVD each year. CVD accounts for nearly 40% of all deaths, which amounts to one death every 33 seconds. It is a leading cause of death for both men and women, and although more common among people aged 65 years or older, the number of sudden deaths from heart disease among people aged 15–34 years has increased. Also, about 61 million Americans, almost one fourth of the population, live with CVD, of which 4.7 million are symptomatic HF patients. This number is expected to increase to an estimated 10 million by 2037, which makes coronary artery disease (CAD) a leading cause of premature, permanent disability in the US workforce. There are almost 6 million hospitalizations each year due to CVD, including HF. The cost of heart disease and stroke in the United States in 2003 was projected to almost match the current federal yearly budget deficit—a staggering $351 billion, including health care expenditures and lost productivity from death and disability. The cost of HF itself is $56 billion a year, 70% of which is due to hospitalization. In a study of 17,000 survivors of hospitalization for HF, it was shown that almost half were readmitted within 6 months, and close to 16% were readmitted at least twice.

**Biology and Physiology of Natriuretic Peptides.** In addition to being an extremely efficient and resilient pump, the human heart is an important endocrine organ that functions together with other physiological systems to control fluid volume. Cells of the heart manufacture a family of structurally related peptide hormones, collectively termed the natriuretic peptides that include atrial natriuretic peptide (ANP) and brain or BNP. Structures of the ANP and BNP are shown in Figure 3 along with a related peptide, C-type natriuretic peptide (CNP). Although CNP is structurally related to ANP and BNP, this peptide is secreted mainly by the vascular endothelium and will not be discussed further. ANP and BNP are encoded by separate genes, and like many physiologically active proteins, are synthesized in the form of precursors. Release of the natriuretic peptides is stimulated by volume overload; these hormones have powerful diuretic, natriuretic, and vascular smooth muscle relaxing actions. The natriuretic peptides are natural antagonists for the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS).

**Biochemistry of Natriuretic Peptides.** The natriuretic peptide system involves secretion of peptides in response to many triggers, including wall stretch,
In fact, fluid overload may cause rapid ventricular dilation and/or increased pressures, all resulting from fluid overload. Activation of the natriuretic system also results from lowering blood volume and blood pressure (BP). Table I presents a listing and summary of the biochemical characteristics of natriuretic peptides.

**Biosynthesis and Secretion of BNP.**

BNP is derived from the 134-aa precursor proproBNP. Upon release stimulation, a 26-aa signal peptide sequence is cleaved from the precursor’s N-terminus to produce proBNP1–76. This hormone is further cleaved by a membrane-bound serine protease (corin), into an N-terminal proBNP1–76 fragment and the active C-terminal 32 amino acid peptide hormone, termed BNP. The N-terminal proBNP fragment has also been proposed as a clinical marker of HF, and clinical application and assays for this proBNP fragment have been developed and recently reviewed.8

BNP is preferentially produced and secreted by the ventricles of the heart without storage in granules. Therefore, regulation of BNP synthesis and secretion occurs mainly at the gene level.9 However, both ANP and BNP can be synthesized in the atrium, ventricles, or both under pathologic conditions. In fact, fluid overload may cause rapid BNP production in both heart chambers, and production in the atrium may exceed the amount of ANP.10

### Table I. Comparison of the Biochemical and Physiological Characteristics of Natriuretic Peptides

<table>
<thead>
<tr>
<th></th>
<th>ANP</th>
<th>BNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptide length</td>
<td>28 Amino acids</td>
<td>32 Amino acids</td>
</tr>
<tr>
<td>Cognate receptor</td>
<td>NPR-A, NPR-C</td>
<td>NPR-A, NPR-C</td>
</tr>
<tr>
<td>Precursor</td>
<td>PreproANP (151 aa)</td>
<td>PreproBNP (134 aa)</td>
</tr>
<tr>
<td>Prohormone (precursor without the signal sequence)</td>
<td>ProANP (126 aa)</td>
<td>ProBNP (108 aa)</td>
</tr>
<tr>
<td>Storage of prohormone</td>
<td>Atrial granules</td>
<td>Preferentially secreted in the ventricle without storage</td>
</tr>
<tr>
<td>Biologically active hormone (containing the disulfide bridge)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>3 Minute</td>
<td>21 Minute</td>
</tr>
<tr>
<td>Release stimulus</td>
<td>Atrial transmural tension</td>
<td>Ventricular wall tension</td>
</tr>
<tr>
<td>Synthesis site</td>
<td>Cardiac atrium</td>
<td>Cardiac ventricle</td>
</tr>
<tr>
<td>Physiological actions</td>
<td>Natriuresis, vasodepression inhibition, RAA system antimitogenesis</td>
<td>Natriuresis, vasodepression inhibition, aldosterone ? antimitogenesis</td>
</tr>
</tbody>
</table>

ANP=atrial natriuretic peptide; BNP=B-type natriuretic peptide; NPR=natriuretic peptide receptors; NT=N-terminus; RAA=renin-angiotensin aldosterone

**Analytical and Assay Characteristics. Preanalytical Determinants.** Which Natriuretic Peptide Should Be Measured, ANP or BNP? Compared with ANP, BNP has emerged as a superior marker for HF and left ventricular (LV) dysfunction. The longer half-life, rapid production and stable release pattern, in addition to activation at the gene level, and the fact that greater amounts are produced in LV tissue has made BNP the marker of choice.9 Physiologically, a two-fold increase in plasma ANP is sufficient to cause negative sodium balance, a fall in systolic and diastolic BP, and an increase in heart rate; however, BNP has a two- to three-fold more powerful effect on natriuresis and BP lowering than ANP.11 Under normal conditions, blood concentrations of BNP are lower than ANP, but as the severity of volume overload progresses, such as, from HF, plasma BNP increases and frequently exceeds ANP concentrations.11 There is a positive correlation between blood BNP concentrations and LV end diastolic pressure, and an inverse correlation to LV function.11 In a study by Cowie et al.,11 BNP showed the greatest predictive power as an indicator of HF when compared with ANP or N-terminus proANP (NT-proANP). For this reason, BNP is considered to be better than NT-proANP, and both have advantages over ANP.

**Physiologic Action of BNP and ANP.**

The main physiological function of the natriuretic peptides is homeostasis and protection of the cardiovascular and other systems from the effects of volume overload. After release into circulation, the effects of BNP and ANP are modulated at target sites in and by the kidney by three specific natriuretic peptide receptors (NPRs). These receptors are located on cell membranes and are termed NPR-A, NPR-B, and NPR-C. After binding the natriuretic peptides, both NPR-A and NPR-B mediate physiologic actions across the membrane through guanylate cyclase, present in a variety of tissues, including the endothelium of large vessels and, for NPR-B, the brain. After binding to the extracellular NPR site, there is transmembrane communication that catalyzes the conversion of guanosine triphosphate to cyclic guanosine monophosphate (cGMP).13 cGMP has potent vasodilatory actions and acts as a second messenger for the natriuretic peptides. In addition to the effects mediated by cGMP, BNP causes a shift in intravascular fluid from the capillary bed into the interstitium,
which induces intravascular volume contraction and a decrease in BP.16-18 In addition, the natriuretic peptides, specifically BNP, may be viewed as natural antagonists of the RAAS because they counteract the sodium conserving, vasoconstriction, and volume retention activities of the RAAS. BNP also appears to inhibit release of renin from kidney cells and aldosterone from adrenal cells, thus limiting the amount of these hormones released. Figure 4 illustrates how the natriuretic peptide system and the RAAS counterbalance each other in regulation of fluid volume and arterial pressure.

BNP and other circulating natriuretic peptides are also degraded by neutral endopeptidase, which opens the ring structure of BNP and ANP, thus inactivating the molecule.19 This endopeptidase has wide tissue distribution, including the kidneys, lung, and brain. The affinity is highest for CNP, followed by ANP which is much higher than for BNP.

Biologic Determinants of BNP Measurements. Blood levels of natriuretic peptides are affected by a variety of physiological factors, such as circadian rhythm, age, exercise, and body posture.5 Drugs including diuretics, angiotensin-converting enzyme inhibitors, adrenergic agonists, sex and thyroid hormones, glucocorticoids, as well as sodium intake, and many clinical conditions can also modify circulating levels of cardiac hormone peptides.

Plasma BNP concentrations increase with age and are higher in women than men both with and without cardiac dysfunction.20,21 The increase in natriuretic peptides with age may be due to the decline in myocardial function typical of senescence22 and/or to reduction in clearance of natriuretic peptides related to the aging process. BNP concentrations for treated hypertensive patients did not show any statistically significant effect from the age-matched control population.20 It has been suggested that age- and gender-specific reference intervals should be considered for routine interpretation of BNP values.

BNP Assays. Initial BNP assays were radioimmunoassays that required an extraction step. They suffered a number of limitations including:

- A delay in reporting results (up to 24 hours were required to complete the assay);
- Highly skilled medical technologists required to perform with high precision;
- Large sample volume; and
- Labor costs are much higher than for automated assays.

Attempts were made to overcome these problems and develop more direct BNP assays.23 Currently, there are four BNP assays that are FDA approved. Some characteristics of the newly developed automated BNP assays are summarized in Table II.

BNP concentration in plasma samples was originally measured by a direct solid phase assay using the Shionoria BNP IRMA kit (Shionogi & Co., Ltd., Osaka, Japan). This sandwich assay employs two different monoclonal
antibodies, which recognize sterically remote epitopes. The measurable range is from 2–2000 ng/L.\textsuperscript{24} The within-day and total coefficient of variations were both 8\% and were consistent across concentrations of BNP.

The currently available BNP assays and their platforms are summarized in Table II. The first BNP assay cleared by the FDA is the Triage BNP Test (Biosite, Inc., San Diego, CA) which is a point-of-care assay, uses whole blood or plasma and produces results in ≈ 15 minutes.\textsuperscript{25} A chemiluminescent sandwich immunoassay (Bayer HealthCare Diagnostics, Tarrytown, NY) for BNP is run on the ADVIA Centaur and ACS:180 platforms. A microparticle-based immunoassay (Abbott Laboratories, Abbott Park, IL) for BNP is run on the AxSYM platform. A chemiluminescent immuno-enzymatic assay (Biosite, Inc., San Diego, CA) for BNP is run on the following Beckman Coulter platforms: Access, Access 2, Synchron LXI and the UniCel Dxi. Another peptide assay is an electrochemiluminescent assay (Roche Diagnostics, Indianapolis, IN) available for measuring NT-proBNP. The reference ranges for BNP and NT-proBNP vary depending on a number of factors. The suggested decision cutpoint for the detection of HF for the BNP assay is 100 pg/mL in the dyspneic patient. For the NT-proBNP assay, the recommended decision cutpoint is 125 pg/mL for both genders under 75 years of age and 450 pg/mL for 75 years and older.

Differences Between NT-proBNP and BNP. While the purpose of this consensus is to offer a review and practical recommendations with regard to mainly BNP, we briefly comment on NT-proBNP, as it has recently been approved by the FDA. While it is likely that both BNP and NT-proBNP will have a place in the diagnosis, prognosis, and management of HF, the two molecules are not identical. Table III lists important differences between BNP and NT-proBNP. Differences that may have clinical relevance are related to excretion, as well as the differences in half-life. While the scope of this paper is such that NT-proBNP will not be discussed at length, it is clear that

| Table II. Characteristics of BNP Assays |
|------------------|------------------|------------------|
| VENDOR | PLATFORM | TECHNOLOGY | MARKER | IMPRECISION | DYNAMIC | CUTOFF (pg/mL) |
|------------------|------------------|------------------|
| Abbott Laboratories, Abbott Park, IL | AxSYM | Microparticle enzyme immunooassay | BNP | Total %CV range: 6.5–9.4 | 0–4000 | 100 |
| Bayer HealthCare Diagnostics, Tarrytown, NY | ADVIA Centaur ACS:180 | Direct chemiluminescent sandwich immunooassay | BNP | Total %CV range: 2.3–4.7 | 0–5000 | 100 |
| Biosite, Inc., San Diego, CA | Triage BNP | Single use fluorescence immunoassay device | BNP | Total %CV range: 9.9–12.2 | 0–5000 | 100 |
| Biosite, Inc., San Diego, CA | Beckman Coulter: Access, Access 2, Synchron LXI, UniCel Dxi | Two-site chemiluminescent immuno-enzymatic assay | BNP | Total %CV range: 2.1–6.7 | 0–5000 | 100 |
| Roche Diagnostics, Indianapolis, IN | Elecsys | Electrochemiluminescent immunooassay | NT-proBNP | Total %CV range: 3.6–5.8 | 0–35,000 | <75 yr: 125 >75 yr: >450 |

BNP=B-type natriuretic peptide; CV=co-efficient of variation; NT=N-terminus; Imprecision is listed in total %CV from vendor package insert.
work is still needed to establish the data and the algorithms to be used in clinical practice with this marker.

Recent reports indicate that there is minimal loss of BNP in blood collected using EDTA as the anticoagulant. BNP is more stable in plastic tubes than glass tubes. Some investigators have indicated that blood can remain at room temperature for up to 48 hours before separation. \(^{26,27}\) BNP has also been found to be stable for several months at \(-20°C\)^{27}; however, whole blood or EDTA plasma specimens are stable for 4–24 hours at room temperature and for 8–24 hours at 4°C depending upon the BNP assay used.\(^{20}\)

### Diagnosis

#### BNP Testing and the Diagnosis of Symptomatic HF. Role of BNP Levels in the Diagnosis of Dyspnea and HF in ED Settings

Although there have been tremendous advances in our understanding of the pathophysiology and treatment of HF, diagnosis of the disease still remains difficult. For the acutely ill patient presenting to the ED with dyspnea, an incorrect diagnosis could place him or her at risk for both morbidity and mortality.\(^{28}\) Therefore, the ED diagnosis of HF must be rapid and accurate. Unfortunately, the signs and symptoms of HF are nonspecific.\(^{29}\) A helpful history is not often obtainable in an acutely ill patient, and dyspnea, a key symptom of HF, may also be a nonspecific finding in the elderly or obese patient in whom comorbidity with respiratory disease and physical deconditioning are common.\(^{30}\)

Routine laboratory values, electrocardiograms, and x-rays are also not accurate enough to always make the appropriate diagnosis.\(^{30–33}\) Multiple studies establish the value of BNP for facilitating the diagnosis of HF in patients presenting with dyspnea. Davis and colleagues\(^{33}\) first measured levels of the natriuretic hormones ANP and BNP in 52 patients presenting with acute dyspnea. They found that admission plasma BNP concentrations more accurately reflected the final diagnosis than did ejection fraction levels or ANP plasma concentrations. Dao et al.\(^{34}\) were the first to use the BNP assay to evaluate 250 patients presenting to an urgent care center with the chief complaint of dyspnea. Physicians assigned to the unit were asked to make an assessment of the probability (low, medium, or high) for each patient with dyspnea and were blinded to the results of BNP measurements. The finding that BNP levels were the strongest predictor of those who had HF served as the foundation for the Breathing Not Properly study,\(^{35}\) the first large-scale, multinational, prospective study using BNP levels to evaluate the causes of dyspnea.

In this study of 1586 patients who came to the ED with acute dyspnea, patients’ BNP levels were measured upon arrival, and the emergency physicians, blinded to BNP levels, were asked to assess the probability of the patient having HF.\(^{36}\) Two independent cardiologists also blinded to the BNP levels later reviewed all clinical data and standardized scores to produce a “gold standard” clinical diagnosis for each patient. BNP levels by themselves were found to be more accurate predictors of the presence

### Table III. B-Type Natriuretic Peptide (BNP) vs. NT-proBNP Assay for Heart Failure

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>BNP</th>
<th>NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyte detected</td>
<td>BNP(^{77–108})</td>
<td>NT-proBNP(^{71–76})</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>3.5 Kilodaltons</td>
<td>8.5 Kilodaltons</td>
</tr>
<tr>
<td>Hormonally active</td>
<td>Yes</td>
<td>No, inactive peptide</td>
</tr>
<tr>
<td>Genesis</td>
<td>Cleavage from proBNP</td>
<td>Cleavage from proBNP</td>
</tr>
<tr>
<td>Half-life</td>
<td>20 Minutes</td>
<td>120 Minutes</td>
</tr>
<tr>
<td>Major clearance mechanism</td>
<td>Natriuretic peptide receptors</td>
<td>Renal clearance</td>
</tr>
</tbody>
</table>
| Increases with normal aging           | + | ++++
| Approved cutoff(s) for CHF diagnosis  | 100 pg/mL | Age <75: 125 pg/mL |
|                                      |     | Age ≥75: 450 pg/mL |
| Available at the point-of-care        | Yes | No |
| Studies completed                     | 1370 | 39 |
| Entry on US market                    | November 2000 | December 2002 |

| NT=N-terminus; CHF=congestive heart failure; \(^{29}\)MedReviews, LLC. Reprinted with permission of MedReviews, LLC. McCullough PA, Sandberg KR. Sorting out the evidence on natriuretic peptides. Rev Cardiovasc Med. 2003;4(suppl 4):S13–S19. Reviews in Cardiovascular Medicine is a copyrighted publication of MedReviews, LLC. All rights reserved.
BNP Consensus Panel 2004

Consensus Statement 2: Using BNP Levels to Help Triage Patients Presenting to the ED With Dyspnea

2.1 BNP is of diagnostic utility in the evaluation of patients with acute dyspnea. Thus, in new patients presenting with dyspnea to an emergency setting, a history, physical examination, chest x-ray, and electrocardiogram should be undertaken together with laboratory measurements that include BNP. Current data suggest the following statements:

2.1.1 As BNP levels rise with age and can be affected by gender, comorbidity, and drug therapy, the plasma BNP measurement should not be used in isolation from the clinical context.

2.1.2 If the BNP is <100 pg/mL, then HF is highly unlikely; negative predictive value, 90%.

2.1.3 If the BNP level is >500 pg/mL, then HF is highly likely; positive predictive value, 90%.

2.1.4 For BNP levels of 100–500 pg/mL, one must consider the following: baseline BNP value elevated due to stable underlying dysfunction; right ventricular failure present from cor pulmonale; acute pulmonary embolism or renal failure.

2.1.5 Patients may present with HF and normal BNP levels or with levels below what might be expected. This can occur in the following situations: flash pulmonary edema, occurring <1–2 hours from symptom onset; HF upstream from the left ventricle (i.e., acute mitral regurgitation from papillary muscle rupture); and obese patients (body mass index [BMI] >30 kg/m²).

2.2 The complementary information that BNP provides may help objectively determine severity of HF and therefore be useful to help triage in deciding whether to admit, transfer to other sites of care, or discharge patients from the ED.
studied patients presenting to the ED with acute dyspnea who were randomly assigned to undergo either a single measurement of BNP or no such measurement. Participating clinicians were advised that a level of BNP <100 pg/mL made the diagnosis of HF unlikely, whereas a level >500 pg/mL made it highly likely. For intermediate levels, use of clinical judgment and adjunctive testing were encouraged. In this single-blind trial of 452 patients, rapid measurement of BNP in the ED was associated with decreases in the rate of hospital admission by 10 percentage points, the median length of stay by 3 days, and the mean total cost of treatment by about $1800, with no adverse effects on mortality or the rate of subsequent hospitalization. This carefully performed trial suggests that the use of BNP testing in the emergency evaluation of acute dyspnea can significantly improve both the quality and cost of care. These results are consistent with the Breathing Not Properly Study and showed that the use of a diagnostic test in the ED can reduce the use of hospital resources and associated costs by eliminating the need for other, more expensive tests, or by establishing an alternative diagnosis that does not require hospitalization.

Comorbidities and Special Issues Which Influence the Interpretation of BNP Levels. Renal Insufficiency. The Breathing Not Properly Multinational Study was pivotal in establishing the correlations between estimated glomerular filtration rate (eGFR) and BNP in those with and without HF. This trial established that BNP values should not be interpreted in isolation and should be integrated with other findings in the diagnostic evaluation. Importantly, chronic kidney disease (CKD) does appear to influence the optimum cut-points for BNP in the diagnosis of HF. In general, as the CKD stage advances, a higher cut-point of BNP is needed. A cut-point of ≈200 pg/mL is reasonable for those with eGFR <60 mL/min. Using this approach, BNP would maintain a high level of diagnostic utility with an area under the receiver-operated characteristic (ROC) curve of >0.80 across all CKD groups.

It is possible that acute HF, with reduced renal blood flow, can result in elevations of serum creatinine and hence a falsely lower eGFR. In addition, chronic volume overload in patients due to CKD with or without HF can result in increased LV hypertrophy and wall tension, thus stimulating secretion of BNP. Multiple studies of systolic HF have demonstrated a decreased survival in those with reduced baseline eGFR. It is unclear whether this is simply due to low cardiac output to the kidneys or if it signifies a unique cardiorenal syndrome conferring increased morbidity and mortality. Multivariate analyses have confirmed an independent relationship...
between renal function and HF mortality; hence, further research into this important relationship is warranted.

Another application of BNP in CKD is measurement of BNP before and after hemodialysis. Several studies have found that BNP is predictably elevated in end-stage renal disease before dialysis and that it drops 20%–40% after a dialysis session.\(^4\) It has been proposed that the BNP reduction ratio could be used as a measure of volume reduction and resultant decreased LV wall tension in those with end-stage renal disease. Current studies are underway to define the expected ranges of the BNP reduction ratio and to understand how it relates to measures of intravascular volume, total body water, and symptom scores.

**Pulmonary Disease With/Without Associated Cardiac Disease.** The presence of concomitant pulmonary disorders does not diminish the utility of BNP in distinguishing patients with HF from those without HF, as long as one uses good clinical judgment and appropriate ancillary testing.

Morrison et al.\(^4\) were able to show that rapid testing of BNP could help differentiate pulmonary from cardiac etiologies of dyspnea. Some types of pulmonary disease, such as cor pulmonale, lung cancer, and pulmonary embolism, have elevated BNP levels, but these patients do not have BNP elevated to the extent of those with dyspnea from HF. In a substudy of Breathing Not Properly\(^3\) (Figure 7), it was demonstrated that of 417 subjects with a history of asthma or chronic obstructive pulmonary disease (COPD) without a history of HF, 21% were found to have newly discovered HF. Only 37% were identified by the clinician in the ED, while a BNP >100 pg/mL identified 93%. Additionally, BNP levels >100 pg/mL provided diagnostic information beyond that obtained from individual chest radiographic indicators.\(^4\)

**Consensus Statement 3: Comorbidities and Special Issues That Influence the Interpretation of BNP Levels**

3.1 There is an alteration in BNP with chronic renal insufficiency (estimated GFR below 60 mL/min), with a likely recalibration of the cutoff value to approximately 200 pg/mL. However, BNP is helpful in the evaluation of dyspnea when it is very low or high. NT-proBNP has a greater correlation with eGFR than BNP, hence levels can be elevated even with the normal age related decline of renal function in the eGFR 60 mL/min–90 mL/min range.

3.2 When the eGFR is below 60 mL/min, NT-proBNP can be considerably elevated and in this setting its utility in the evaluation of HF is unknown.

3.3 Baseline BNP levels might therefore be important in dialysis patients, as changes above baseline likely represent changes in volume. Thus a pre-dialysis BNP level might help determine the amount of volume to be removed. As of now, there is no good evidence that monitoring BNP levels during dialysis will help make correct decisions as to how long one should keep dialysis going. The effect of renal insufficiency on BNP may help determine the intensity of dialysis therapy.
Because BNP levels have been a useful surrogate of wedge pressure and are useful in differentiating noncardiogenic from cardiogenic pulmonary edema. BNP levels were obtained in 35 patients with acute respiratory distress syndrome (ARDS) and from 42 patients hospitalized for severe dyspnea with the diagnosis of HF. The median BNP level in patients with HF of 773 pg/mL was significantly higher than patients with ARDS (123 pg/mL; p<0.001) (Figure 8). The area under the ROC curve using BNP to differentiate HF from ARDS was 0.90 (0.83–0.98; p<0.001). At a cut-point of 360 pg/mL, there was 91% sensitivity, 86% specificity, 89% positive predictive value, and a 94% negative predictive value (accuracy=88%) for ARDS vs. HF. In the Breathing Not Properly Multinational Study, there were 417 patients who had a history of lung disease and no history of HF who presented with acute dyspnea. The final adjudicated diagnosis was HF in 20.9% of cases.

Approximately one third of these “latent HF” cases were identified by the emergency physician, one third had cor pulmonale, and one third appeared to have the wrong diagnosis by past history and current ED evaluation. Importantly, BNP at a cut-point of 100 mg/dL would have identified 93.1% of these cases. Thus, in patients with established lung disease (COPD or asthma), when BNP is added to the dyspnea evaluation, it provides a yield of approximately 20% for latent HF. The diagnoses now present therapeutic opportunities for HF therapy including agents which block the RAAS, diuretics, and β blockers as tolerated.

In a study of 110 angiographically proven pulmonary emboli cases, one third of the patients had a BNP level ≥75 pg/mL. Importantly, these cases with an elevated BNP in the upper normal range or above 100 pg/mL had a higher mortality than the first two tertiles of BNP values of <8.7 pg/mL and 8.7–75 pg/mL, respectively. Furthermore, in an echocardiographic study, BNP elevations were associated with right ventricular (RV) dilation and dysfunction due to pressure overload in the setting of pulmonary embolism. It appears that BNP will not be an adequate screening test for pulmonary embolism; however, in the setting of a suspected or confirmed embolic event, an elevation of BNP indicates RV pressure overload and a higher overall mortality.

Finally, BNP levels are closely related to functional impairment of patients with primary pulmonary hypertension and parallel the extent of pulmonary hemodynamic changes and right HF. It is speculated that serial measurements of BNP may help improve the management of these patients.

**Consensus Statement 4: Role of BNP in Pulmonary Disease With/Without Associated Cardiac Disease**

**4.1** In approximately 20% of patients with pulmonary disease, BNP will be elevated implying combined HF and lung disease, cor pulmonale, or a misdiagnosis when the true etiology of dyspnea is HF.

**4.2** In the setting of pulmonary embolism, BNP will be elevated in one third of cases and is associated with right ventricular pressure overload and higher mortality. BNP is not diagnostic for acute pulmonary embolism. A high BNP level in the setting of acute pulmonary embolism is prognostic of a worse outcome, especially when associated with high troponin levels.

**4.3** The role of BNP levels in chronic pulmonary hypertension remains to be determined. Pulmonary disease which results in pulmonary hypertension and right ventricular pressure or volume overload can lead to elevated BNP levels, usually in the range of 100–500 pg/mL.

**Diastolic Dysfunction.** Diastolic dysfunction, which is a common cause of HF in patients presenting with dyspnea, is also associated with high BNP levels. In the Breathing Not Properly Study, BNP levels were roughly half as high as for patients with systolic dysfunction (Figure 9). Interestingly, the BNP elevations in diastolic dysfunction were similar in magnitude to those patients with mitral valve restrictive-like filling patterns. A number of studies have elucidated the value of BNP levels to detect diastolic dysfunction. Recently, Lubsen et al. assessed BNP levels in 294 patients referred for echocardiography. Patients diagnosed with evidence of abnormal LV diastolic function (n=119) had a mean BNP concentration of 286±51 pg/mL, while the normal LV group (n=175) had a mean BNP concentration of 33±3 pg/mL. Patients with restrictive-like filling patterns on echocardiography had...
the highest BNP levels (408±66 pg/mL), and patients with symptoms had higher BNP levels in all diastolic filling patterns. The area under the ROC curve for BNP to detect any diastolic dysfunction was 0.92 (0.87–0.95; p<0.001). A BNP value of 62 pg/mL had a sensitivity of 85%, specificity of 83%, and an accuracy of 84% for detecting diastolic dysfunction when systolic function was normal. In the future, therapeutic trials for treating patients with diastolic dysfunction will likely consider including BNP levels as an enrollment criterion and a potential end point for treatment.

Obesity. Obesity is now known to adversely influence systolic and diastolic ventricular function and participate as an important risk factor for the development of CAD and heart failure. Physiologically, natriuretic peptides and lipolysis have been closely linked, and adipose tissue is intimately related to the natriuretic clearance receptor. This suggests that pathophysiologic mechanisms underlying the relationship between obesity and CVD outcomes could at least partially be related to aberrancies in the natriuretic peptide system, in the clinical realm, the presence of obesity can interfere with the usual diagnostic approach to HF. In particular, signs and symptoms of volume overload can be difficult to ascertain in the obese individual with HF. In such circumstances, establishing the adjunctive diagnostic utility of BNP for the diagnosis of HF is of great importance because of the possibility that obesity might influence the peripheral expression of natriuretic peptides. Mehra and colleagues first demonstrated that obesity influences the expression of BNP in chronic HF. These investigators found a significant inverse relationship between body mass index (BMI) and BNP levels. These lower levels of BNP in patients with obesity (BMI >30 kg/m²) were noted despite a similar degree of severity of HF controlled by functional class, peak aerobic capacity and circulating cytokines) among lean and obese patients (Figure 10). Furthermore, nearly 40% of the obese patients in this study demonstrated BNP levels that were below the threshold of abnormality (<100 pg/mL). Mehra’s data are supported by the Breathing Not Properly Study. In this study, patients presenting with HF and low BMI had BNP levels >1000 pg/mL 50% of the time while the obese patients presenting to the ED had BNP levels >1000 pg/mL only 8%–24% of the time. These data have been extended to those obese patients without HF as well as in a recent investigation from the Framingham Heart Study.

Figure 10. Relationship of B-type natriuretic peptide (BNP) level in lean, overweight, and obese patients. Reprinted with permission from J Am Coll Cardiol. 2004;439:1590–1595.

Prognosis
BNP in Prognostication and Risk Stratification in Outpatients With HF. Elevations of BNP have been shown to be a powerful marker for prognosis and risk stratification in the setting of HF. In a recent study of 78 patients referred to an HF clinic, BNP showed a significant correlation to the HF survival score. However, it appears that BNP levels are not related to self-reported measures of health status or quality of life, since patients adjust their

Consensus Statement 5: BNP in Diastolic Dysfunction

5.1 BNP may be used to detect patients with diastolic dysfunction. Elevated levels of BNP along with diastolic filling abnormalities might help to reinforce the diagnosis of diastolic dysfunction.

5.2 BNP concentrations above age-adjusted cut-points may identify elderly patients with diastolic dysfunction.
expectations downward as they become more ill. Hence, BNP levels can be supportive of the New York Heart Association (NYHA) functional classification, which is physician assigned, and give complementary information to the symptoms reported by the patient (Figure 11). Harrison et al. followed 325 patients for 6 months after an index visit to the ED for dyspnea (Figure 12). Higher BNP levels were associated with a progressively worse prognosis. The relative risk of 6-month HF admission or death in patients with BNP levels >230 pg/mL was 24 times the risk of levels less than this.

These small, single center studies were validated in a recent analysis of the Valsartan in Heart Failure Trial (Val-HeFT) (Figure 13). Val-HeFT evaluated the role of valsartan in moderate to severe HF, and represents the largest collection of neurohumoral data in HF patients. BNP was measured in all patients at randomization, with follow-up values measured at 4, 12, and 24 months thereafter. Patients with a BNP level above the median had a relative risk of 2.1 for mortality, and 2.2 for first morbidity events, in comparison to those with BNP levels below the median. Furthermore, there was an incremental increase in relative risk of mortality and morbidity throughout each quartile (<41 pg/mL, 41–97 pg/mL, 97–238 pg/mL, and >238 pg/mL) of BNP levels. There are several important inferences from this analysis: 1) approximately half of well-treated HF patients had BNP levels <100 pg/mL when measured as outpatients; 2) the lowest quartile of BNP (<41 pg/mL) had the lowest all-cause mortality; 3) the highest quartile (>238 pg/mL) had the highest mortality of 32% at 30 months. Importantly, change from baseline and the percent change of BNP level over a 4- and 12-month period were also evaluated. This analysis demonstrated a direct relationship between percent change from baseline BNP levels and 4-month mortality. Highest mortality was seen in patients with the largest percent increase in BNP, while the lowest mortality was observed in those with the largest percent decrease in BNP.

BNP Levels and Prognosis in Hospitalized Patients. Several recent trials support the usefulness of changes in BNP levels, as well as predischarge BNP levels, as important markers to optimize the care of patients hospitalized with HF. Bettencourt et al.

Consensus Statement 6: BNP in Obesity

6.1 Since obese patients (body mass index [BMI] >30kg/m²) express lower levels of BNP for any given severity of HF, caution should be exercised in interpreting BNP levels in such patients.

6.2 In obese patients with HF, it is likely that BNP levels followed serially might continue to provide an accurate index of HF stability.
investigated the ability of changes in BNP levels during hospitalization to track clinical outcomes in 50 consecutive patients hospitalized with decompensated HF. BNP levels decreased in most patients, but to a significantly greater degree in those who remained free of later readmission for cardiovascular causes and death. Of the seven patients with increases in BNP during hospitalization, only one patient was event free at 6 months. Within the subgroup of patients with declining BNP levels during hospitalization, the degree of change in BNP tracked 6-month outcomes. In patients without 6-month hospital readmission or death, BNP levels fell from 619+491 pg/mL to 328+314 pg/mL (p<0.0001). In comparison, changes in BNP levels were less pronounced in those who suffered events, with BNP levels decreasing from 779+608 pg/mL to 643+465 pg/mL (p=0.08) in this group. Similar results were reported by Cheng et al., in their analysis of 72 patients admitted with decompensated NYHA Class III–IV HF. Of the 72 patients admitted with HF, 22 patients developed 30-day rehospitalization or death. The BNP levels increased by 233 pg/mL in these patients, in comparison to a 215 pg/mL decrease in those who remained free of 30 day adverse events. Finally, Logeart and colleagues demonstrated that HF patients who had a predischARGE BNP level >700 ng/L, had an 80% rate of death or hospitalization at 120 days (relative risk=15.2) (Figure 14). Conversely, those with BNP values <350 ng/L had a <10% rate of death or rehospitalization over the same period. In summary, blood BNP levels appear to have powerful prognostic capabilities when measured on admission and on the day of discharge. A favorable pattern for patients is a fall in BNP of >50% from the admission level, or a BNP <350 pg/mL on the day of discharge. Patients with elevations of BNP values during hospitalization, or with values >500 ng/mL on the day of discharge, have high event rates and warrant careful attention for maximizing medical therapy and close follow-up.

**BNP and the Prediction of Sudden Cardiac Death.** Several studies suggest that BNP by accurately reflecting acute ventricular filling pressures, dilatation, and stretch, may indicate risk for ventricular arrhythmias and sudden cardiac death. This association was most impressively demonstrated by Berger et al., who, in 452 ambulatory patients with mild to moderate HF (NYHA functional classes I and II) and LV ejection fraction less than 35%, found that BNP levels independently predicted sudden cardiac death. In that study, BNP >130 pg/mL separated patients with high vs. low rates of sudden death. Furthermore, only 1% (1 of 110) of patients with a BNP level <130 pg/mL died suddenly compared with 19% (43 of 227) of patients with BNP levels >130 pg/mL. Additional evidence that elevated levels of BNP portend ventricular arrhythmias is indirect. Cardiac resynchronization therapy (CRT) is increasingly recognized to improve symptoms and reduce mortality in patients with moderate to severe HF and ventricular asynchrony. Many studies have shown that BNP concentrations fall when CRT therapy is initiated and rise when CRT is subsequently deactivated. Studies have also shown that CRT reduces the incidence of ventricular arrhythmias. Higgins et al. studied 32 patients in whom CRT devices with defibrillator capability were implanted. The study population had a mean age of 65±10 years, 70% had CAD, and all had HF (22% were in NYHA functional class II, 65% in functional class III, and 13% in functional class IV. During a 6-month crossover of CRT-activated to CRT-deactivated therapy, the authors found that patients experienced significantly fewer appropriate device therapies when CRT was activated than when it was not.

**Association of BNP With Cardiac Troponin I in HF.** There is increasing evidence that myocyte necrosis and apoptosis contribute to progressive LV dysfunction in HF. Several studies have reported elevation of cardiac troponin in patients with decompensated HF in the absence of acute coronary syndrome (ACS) or CAD. Recently, Fonarow’s group analyzed 251 HF patients referred to the UCLA Cardiomyopathy Center. Troponin I levels were drawn at the time of initial presentation (level of detection 0.04 ng/mL) along with BNP levels. Survival was measured from the date of initial evaluation. The primary end
point was mortality or need for urgent transplantation. Figure 15 shows that in the setting of HF, both troponin I and BNP were independent predictors of survival in HF. The two together gave additive prognostic risk.

Natriuretic Peptide Hormone Measurement in ACS/CAD. Cross-sectional studies have demonstrated statistically significant elevation in natriuretic peptide levels among patients presenting with unstable angina and no evidence of myocardial necrosis. When considered in the context of the experimental studies described above, these findings suggest that myocardial ischemia, even in the absence of necrosis, is sufficient to cause release of BNP and NT-proBNP. When compared with patients with HF, however, those with ischemia as the “trigger” for BNP release have more modest elevations of plasma BNP and NT-proBNP, and there is considerable overlap between normal and disease patients. Sensitivity and specificity for BNP will not be adequate to diagnose ischemia because many patients with unstable angina do not have BNP elevation and the levels detected among those with elevation are similar to those seen in other conditions, such as asymptomatic LV dysfunction and pulmonary embolism.

In contrast, recent studies demonstrate that BNP or NT-proBNP elevation among patients with unstable angina and non–ST-segment elevation MI is associated with powerful and independent predictive value. In a linear fashion, increasing levels measured approximately 40 hours after the onset of ischemic symptoms, in a multicenter trial evaluating biomarkers in ACS patients. The findings suggest the important prognostic value of biomarkers across the entire spectrum of patients presenting with the ACS.

Recent publication examined baseline NT-proBNP levels in a multicenter trial evaluating biomarkers in ACS patients. The findings suggest the important prognostic value of biomarkers across the entire spectrum of patients presenting with the ACS.

A study from the MONItoring of Trends and Determinants of Cardiovascular Diseases (MONICA) cohort assessed the utility of BNP in identifying LV dysfunction in 1252 community-based patients aged 25–74 years of age. A plasma BNP concentration of 17.9 pg/mL was found to have a sensitivity of 76% and a specificity of 87% for LV dysfunction as defined by an LV ejection fraction <30%. The overall negative predictive value was 97%, but the positive predictive value was only 16%. In a community-based prospective cohort of 2177 participants from the Framingham study, the performance of BNP for the detection of LV hypertrophy or systolic dysfunction was suboptimal, suggesting limited usefulness of BNP as a mass screening tool. Because of the low prevalence of disease in many of these patient groups and the age- and gender-related changes in BNP levels, screening low-risk populations may not be feasible.

The same investigators, however, examined the long-term prognostic importance of the levels of ANP and BNP in asymptomatic middle-aged persons from the Framingham Offspring Study. After adjusting for traditional risk factors, Wang and colleagues found that the level of BNP was independently predictive of the risk of death, HF, atrial fibrillation, andstroke over a mean follow-up period of about 5 years. Levels of BNP above the 80th percentile in this cohort (i.e., higher than 20 pg/mL) were associated with an increase by more than 60% in the long-term risk of death. Furthermore, there was a significant
prognostic gradient with respect to the risk of HF; atrial fibrillation, and stroke among the three levels of BNP (low, intermediate, and high) examined. This remarkable finding suggests that in the asymptomatic community-based cohort, there are important prognostic data even in the range of BNP levels <100 pg/mL, the level used to rule out HF in 90% of acutely dyspneic patients.

Screening in the Higher-Risk Populations. Silver and Pisano84 using traditional cut-points, found a high incidence of elevated BNP levels in an unselected at-risk population in a community-based setting. This, along with other emerging evidence, suggests that BNP may additionally serve as an important screening tool to detect patients progressing from Stage A to Stage B in the HF natural history pathway. This suggests that using lower cut-points of BNP along with other historical, clinical, and laboratory information is likely to lead to more appropriate evaluation and triage of these patients.

In the population-based Hillingdon HF Study,85 one third of patients referred to a rapid-access clinic by a primary care physician with a new diagnosis of HF had the diagnosis confirmed on further assessment. The diagnostic value of the plasma BNP concentration compared with the clinical opinion of an expert panel was very high. The area under the ROC curve for plasma BNP was 0.96, compared with 0.79 for cardiothoracic ratio. Taking a cutoff value of 22 pmol/L (76.4 pg/mL) combined a very high negative predictive value (98%) with an acceptable positive predictive value of 70%, a sensitivity of 97%, and specificity of 84%. Therefore, this study suggests there is a potential for the BNP test to improve the efficiency of referring patients for further assessment.

Epshteyn et al.86 found that in a high-risk but asymptomatic diabetic population, a BNP cut-point of about 40 pg/mL could detect underlying systolic and diastolic dysfunction. Atisha et al.87 found only rare and mild cases of cardiac dysfunction (mainly diastolic) in patients undergoing echocardiography whose BNP levels were <20 pg/mL. Recently, Heidenreich et al.88 found that screening patients with BNP using a cutoff of 24 pg/mL followed by echocardiography was economically attractive for 60-year-old men and possibly for women for patient groups with at least a 1% prevalence of moderate or greater LV systolic dysfunction (ejection fraction <40%). Screening all patients with echocardiography was expensive, but sequential BNP-echocardiography screening strategy was economically attractive.

### Consensus Statement 7: BNP Measurement in Sudden Death, Acute Coronary Syndrome, and Coronary Artery Disease

7.1 BNP is a significant independent predictor of mortality in HF. Changes in BNP over time are associated with morbidity and mortality. This provides physicians with an opportunity to provide more aggressive treatment to these patients.

7.1.1 Several studies suggest that BNP levels are predictive of sudden cardiac death. Thus, BNP levels might help us further stratify patients who might most benefit from newer therapies, such as implantable cardiac defibrillators.

7.1.2 Additional biomarkers (troponin, and C-reactive protein) may provide unique, adjunctive, and independent information to a BNP measurement with regard to patient outcomes.

7.1.3 When used together in a combined strategy, BNP and cardiac troponin provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF and acute coronary syndrome. Such information is likely to enhance our ability to appropriately triage higher-risk HF patients and more reliably identify low-risk HF patients who may be candidates for less intensive evaluation and therapy.

7.1.4 In the setting of ACSs, low-level troponin elevation is highly predictive of recurrent ischemic events, whereas BNP appears to be a “pump failure” marker, more closely associated with death and HF progression. Using these two markers together improves the detection of patients at risk for adverse events.

7.1.5 In the future, BNP will likely be included in multi-marker panels that include troponin and C-reactive protein, as each of these markers provides unique and independent information with regard to patient outcomes.

7.2 When used together in a combined strategy, BNP and cardiac troponin provide a more effective tool for identifying patients at increased risk for clinically important cardiac events related to HF and acute coronary syndrome. Multi-marker panels that include BNP, troponin, and C-reactive protein are now available and each of these markers provides unique and independent information with regard to patient outcomes.
Treatment Monitoring

BNP Levels in the Hospitalized Patient. There are approximately 1 million admissions annually to US hospitals for HF. While patients who are admitted to the hospital with decompensated HF often have improvement in symptoms with the various treatment modalities available, there has been no good way to evaluate the long-term effects of the short-term treatment. Readmission after hospitalization for HF is surprisingly common, estimated at 44% at 6 months within the Medicare population. Considering that hospitalization is the principal component of the cost for patient care (70%–75% of the total direct costs), a reduction in HF hospitalizations is an appropriate goal for whatever treatment modalities are in place.

Though not yet an FDA-approved indication, the use of BNP for targeting treatment of patients with HF is under active investigation. Targeting treatment of disease has precedent—treatment of hypertension is targeted to BP, diabetes to blood sugar, and hypercholesterolemia to cholesterol levels. The fact that BNP has a short half-life, has easy-to-measure levels, and is a surrogate for wedge pressure, volume, NYHA functional class, and prognosis suggests its usefulness as a guide to therapy in HF.

Does High BNP Always Mean High Filling Pressure? Since a major stimulus for the release of BNP is increased wall tension, one might expect that BNP levels would correlate with elevated LV filling pressures. Indeed, there is a body of data to support that supposition. However, in the clinical setting there are many occasions where high BNP level is not associated with high filling pressures. Some of these situations include BNP elevations from right-sided failure secondary to cor pulmonale, pulmonary embolism, or primary pulmonary hypertension; acute or chronic renal failure; and rapid lowering of the wedge pressure with diuretics and/or vasodilators before a Swan-Ganz catheter is placed. Additionally, under some circumstances, BNP levels might be normal when the wedge pressure is high. This would most likely occur in acute mitral regurgitation where the increase in capillary pressure is upstream from the left ventricle and in “flash” pulmonary edema, where the BNP might not have had time to be synthesized.

This would most likely occur in acute mitral regurgitation where the increase in capillary pressure is proximal to the left ventricle and in “flash” pulmonary edema, where the BNP might not have had time to be synthesized due to the short time from symptom onset.

In a given patient the BNP level does not always correlate to wedge pressure. However, in a patient admitted with HF and high filling pressures secondary to volume overload, along with a high BNP level (“wet BNP” see below), a treatment-induced decrease in wedge pressure will almost always be associated with a rapid drop in BNP level, as long as the patient is maintaining adequate urine output. Kazanegra et al. measured wedge pressure, hemodynamic measurements (pulmonary capillary wedge pressure [PCWP], cardiac output, right atrial pressure, systemic vascular resistance), and BNP levels every 2–4 hours for the first 24 hours and every 4 hours for the next 24–48 hours in patients admitted for decompensated HF. PCWP dropped from 33±2 mm Hg to 25±2 mm Hg over the first 24 hours, while BNP dropped from 1472±156 pg/mL to 670±109 pg/mL (Figure 17). The correlation between BNP levels and other indices of cardiac function—cardiac output (thermodilution), mixed venous oxygen saturation, and systemic vascular resistance was nonsignificant. It should be emphasized that patients with end-stage HF admitted for transplant workup who are not acutely volume overloaded may not demonstrate a decline in BNP levels as the wedge pressure is lowered (“dry BNP”).

---

Consensus Statement 8: BNP Screening in Higher-Risk Populations

8.1 At this time, BNP testing is not appropriate for screening asymptomatic, low-risk populations for LV systolic dysfunction.

8.2 There may be some value in using plasma BNP to screen high-risk subgroups of the population such as postMI patients, diabetic patients, or those with an extended history of uncontrolled hypertension. It is important to note that echocardiography is likely to remain the main method of assessing LV function in this setting.
Compensated and Decompensated BNP Levels. The BNP level of a patient who is admitted with decompensated HF is comprised of two components: that of a baseline, compensated, “dry” BNP level and that occurring from acute pressure or volume overload (decompensated or “wet” BNP level). At the point of decompensation, a patient’s BNP level will be a sum of their baseline BNP level plus what volume overload adds a sum of baseline BNP plus the additional production of BNP from ventricular stress due to acute volume overload.

The lower the discharge “dry weight” or compensated BNP level is, the less likely that the patient will be an early victim to rehospitalization. This is because a low BNP level (<200–300 pg/mL) represents an NYHA functional class II patient and one that is more likely to be in a true euvolemic state. Knowing a patient’s baseline compensated or “dry weight” BNP level is likely to be important in monitoring the patient in the first 30 days after discharge. Early elevations of BNP over baseline soon after discharge may trigger the need for more intensive outpatient management and therapy.

Stevenson has published a rapid assessment of hemodynamic status to stratify patients to treatment to diuretics, vasodilators, or inotropic agents. Patients who are admitted to the hospital with either new-onset or decompensated HF are usually volume overloaded. Treatment in this setting includes diuretics and vasodilators when patients are “wet and warm.” In general, almost all these patients have BNP levels >600 pg/mL. In fact, if BNP levels were less than this, one should carefully consider other methods to ascertain a patient’s volume status and/or caveats to BNP interpretation (see above).

Diuretics, inotropes, and vasopressors are often indicated when patients are classified as “wet and cold.” These patients frequently have BNP levels >1000 pg/mL. Patients that are “cold and dry” have BNP elevations secondary to systolic dysfunction, but perhaps BNP levels are not as high as the “cold and wet” patients. Finally, patients who are “warm and dry” are likely to have lesser elevations of BNP levels.

Pitfalls and Caveats in BNP Interpretations. There are circumstances whereby plasma BNP levels may be affected by ambient biological conditions or disease unrelated to HF. Plasma BNP tends to be higher in the elderly, in women, in renal insufficiency, immediately following exercise, and after open heart surgery. There are mixed reports of altered BNP levels with atrial fibrillation and thyroid disease, but it can be increased in hyper- and hypothyroidism, and in some patients with atrial fibrillation. More research is necessary.

Plasma BNP can be evaluated in patients with acute, life-threatening illness such as sepsis and toxemia of pregnancy. The mechanism of these alterations in plasma BNP in these patients is not clear, but heightened BNP may not be due to “congestive HF.”

Low plasma BNP levels have been reported in patients with stable, ambulatory HF. In a subset of patients with symptomatic but stable HF due to dilated cardiomyopathy, plasma BNP levels were found to be below what would be considered “normal” (<100 pg/mL). The BNP test cannot replace or supersede the judgment of the clinician, as the diagnosis of HF requires clinical evaluation. The importance of the context in which BNP is measured cannot be overstated. A normal plasma BNP in a patient presenting to the ED with dyspnea has more negative predictive power than a “normal” plasma BNP in a patient with stable, chronic HF.

How Often Should One Obtain a BNP Level in the Hospital? This is an often-asked question with no single right answer. Certainly, as one becomes more experienced in using BNP levels in the hospital, one will likely tailor requests for blood draws at admission and discharge and after any major clinical change, either for better or for worse. One author (ASM) obtains a BNP level after 24 hours of treatment. Failure of BNP levels to fall in a 24-hour period may delineate a high-risk patient who should receive more vigorous treatment. If a very sick patient is being treated in the intensive care unit without Swan-Ganz guidance, perhaps more frequent assessment of BNP levels (every 4–6 hours) is warranted. During nesiritide infusion, BNP levels do not need to be measured (measure would be sum of endogenous plus exogenous). However, exogenous BNP should be cleared within 2 hours following infusion. Since the half-life is 22 minutes, 4 half-lives will then represent the new steady state and one will have reached 96% of the change in levels by this time. Delay in analysis beyond this time frame will only provide changes that are smaller than the coefficient of variation of the assay.

What if a BNP Level Does Not Fall During Hospitalization? There may be several explanations why elevated BNP levels do not fall with treatment in some patients with HF. First and foremost, the high BNP level may actually be the patient’s “dry” BNP level and will not be acutely lowered with diuretics or vasodilators. These patients tend to be NYHA functional class IV and have a poor prognosis.

Secondly, a consideration of the differential diagnosis must be entertained. Patients at their hemodynamically dry weight with a BNP of 700 pg/mL, but with a new superimposed pulmonary embolus, may demonstrate severe dyspnea and no response to HF therapy. Perhaps patients who have high BNP levels that do not respond to treatment should be considered for other more invasive types of therapies such as cardiac transplantation or use of ventricular assist devices. Patients with a wide QRS might be considered for biventricular pacing. In a recent trial of patients who received ventricular assist devices for end-stage HF, BNP levels appeared to fall as remodeling of the heart occurred, and an early decrease in BNP plasma concentration was indicative of recovery of cardiac function during mechanical circulatory support. In any event, patients with high BNP levels at discharge are at increased risk, and if nothing else, are candidates for early follow-up and perhaps home nursing visits.
There are other reasons that a BNP level might not fall with treatment. It is possible that with parenteral diuretic treatment of the decompensated, pre-renal patient, further azotemia might occur. This will likely down-regulate BNP clearance receptors, and BNP levels will rise. In this setting, nesiritide infusions might be indicated. Another possible scenario is that a patient with left and right HF and significant ascites and/or edema, may often diurese many liters before BNP levels actually drop. This is possibly because rather than lowering wedge pressure, the urine output is occurring secondary to mobilization of third space fluid. Continuing diuresis and/or vasodilatation should eventually lower BNP levels. Finally, acute, severe pressure or volume overload might turn on the transcription of the mRNA for BNP to such a degree, that even upon initial lowering of the wedge pressure, BNP levels might still be increasing.

BNP and Heart Transplantation. Since BNP reflects ventricular wall stress and pressure, levels of this hormone in heart transplant recipients have been studied as a candidate marker of allograft function. Early case-controlled studies in heart transplantation suggested that stable recipients demonstrated elevated BNP levels. Buckley et al. hypothesized that the difference in baseline BNP levels between the controls and transplant recipients could be attributed to higher systemic BP, older age, and decreased renal function of the transplanted cohort. Arionu et al. examined the ventricular expression of BNP by evaluating endomyocardial biopsy specimens and demonstrated a linear relationship between plasma and ventricular BNP levels (r=0.8, p<0.05), thus finding that elevated levels of BNP are detectable in the RV myocardium of the transplanted heart. The same group also demonstrated elevated BNP gene expression at the mRNA level compared with control subjects. To negate any effects from cardiac surgery per se for causing the difference in the BNP level, Gery et al. utilized post-bypass patients as controls and reported the same findings as previous investigators, confirming that the elevated BNP level found among transplant recipients is not related to the surgery but to physiological changes in the transplanted heart. Park et al. analyzed 237 consecutive BNP levels in 87 stable adult heart transplant recipients, representing the largest study to date. While mean BNP level among the cohort was 258±276 pg/mL, the median value was significantly lower (153 pg/mL). These findings suggest a three- to four-fold elevation in “stable” cardiac allograft recipients and demonstrate that despite an observed normal systolic performance, the transplanted heart persistently manifests restrictive or relaxation abnormalities resulting from the process of engraftment and ongoing effects of rejection (insidious or overt), hypertension or RV aberrations. Mehra and colleagues found that a BNP level >250 pg/mL in chronic survivors is closely related with allograft failure; the development of CAD; and pointed to an increased likelihood of cardiac death (Figure 18).

Therapy/Administration as a Therapeutic Agent
B-Type Natriuretic Peptide as a Therapeutic Agent for Decompensated HE. In addition to being a suitable marker of CVD that bears both diagnostic and prognostic importance in HF, B-type natriuretic peptide is a rational therapeutic option again because of its primordial homeostatic functions. [For the sake of clarity, the therapeutic applications of BNP will be denoted as B-type natriuretic peptide.]
The pleiotropic effects of B-type natriuretic peptide, including vasodilatory, natriuretic, diuretic, antifibrotic and lusitropic properties, make it an especially attractive option in the management of acute decompensated HF (ADHF). The adjunctive ability of B-type natriuretic peptide to inhibit the renin angiotensin system, inhibit the release of aldosterone, block the effects of endothelin, and promote central sympatho-inhibitory tone, adds further to its salutary properties.

HF is an insidious clinical syndrome that is initiated by overt cardiac injury either acute (MI) or chronic (e.g., hypertension), but perpetuated by ongoing neurohormonal activation. The initial benefit of stimulation of the RAAS and the sympathetic nervous system is to preserve blood flow to critical organs and support systemic BP through vasoconstriction and salt and water retention. Angiotensin II is a vasoconstrictor and growth-promoting neurohormone. It promotes increased sodium reabsorption in the proximal tubule. Angiotensin II also stimulates the production of tumor necrosis factor-α and transforming growth factor β-1—both of these cytokines lead to enhanced growth stimuli for cardiac myocytes. Norepinephrine provokes vasoconstriction and is especially toxic to the myocardial cell. The protean role of aldosterone is becoming increasingly apparent.

In addition to promoting sodium reabsorption from the distal collecting tubule, it is now evident that aldosterone leads to collagen matrix turnover, promotes cellular inflammation, and potentiates the effects of catecholamines. Endothelin-1 is perhaps the most potent vasoconstrictor yet described. Endothelin-1 increases cardiac afterload, decreases glomerular filtration rate, and stimulates myocyte hypertrophy. It has been demonstrated in an incontrovertible manner that the extent of neurohormonal derangement parallels the severity of underlying LV dysfunction and HF. It is also apparent that angiotensin II, norepinephrine, aldosterone, and endothelin are all associated with direct myocardial toxicity, and among other effects, stimulate fibrosis, remodeling, and generate ventricular arrhythmias. When this process proceeds in an unabated manner, LV dysfunction progresses and worsening HF ensues.

The discovery of a natriuretic effect of atrial tissue extracts by de Bold in 1981 has led way to discovery of the countervailing properties of the natriuretic peptide system and its therapeutic potential. Remarkably, there is evidence that B-type natriuretic peptides exert a counterbalancing influence on many of the foregoing deleterious consequences of neurohormonal activation.

B-type natriuretic peptide binds to a family of natriuretic peptide receptors located on endothelial and smooth muscle cells, specifically NPR-A, NPR-B and NPR-C. The function of NPR-C is largely as a clearance receptor. The physiological properties of B-type natriuretic peptide are thus mediated by both NPR-A and NPR-B. The union of B-type natriuretic peptide to NPR-A and NPR-B results in the generation of 3′ 5′cGMP. cGMP is felt to be the second messenger through which the favorable properties of B-type natriuretic peptide occur. In the kidney, B-type natriuretic peptides increase glomerular filtration and inhibit sodium reabsorption leading to a natriuresis and diuresis. In addition, B-type natriuretic peptide inhibits renin secretion and directly inhibits the release of aldosterone from adrenal cortical cells. In the periphery, B-type natriuretic peptide relaxes smooth muscle causing vasodilation. At the heart, B-type natriuretic peptide improves coronary blood flow and exerts a lusitropic effect on the left ventricle. This favorable cascade of effects of B-type natriuretic peptide appears to be overwhelmed in HF either because of the extent of pathobiological neurohormonal activation, enhanced clearance of B-type natriuretic peptide, abnormal protein synthesis, or reduced receptor affinity. As such, efforts to up-regulate the effects of B-type natriuretic peptide have been pursued with a focus on the exogenous administration of B-type natriuretic peptide (a.k.a. nesiritide [Natrecor Scios Inc., Fremont, CA]).

The ideal candidate drug for ADHF ought to be one that improves the deranged hemodynamics in ADHF, promotes a diuresis, has minimal effect on myocardial oxygen consumption, does not possess inotropic activity, is not proarrhythmic, and does not contribute to further neurohormonal activation or additional ventricular remodeling.

Current Therapies for ADHF. Diuretics are clearly beneficial in the setting of ADHF as they quickly and effectively lower filling pressures. However, an emerging database is now demonstrating very worrisome consequences of excessive diuretic exposure. Diuretics lead to contraction of effective arterial blood volume, which is a further stimulus for renin production and subsequent angiotensin II production. The usual flux in electrolytes is also problematic as it engenders ventricular rhythm disturbances, some of which may on
occasional be quite serious. Remarkably, there have been no data demonstrating a survival advantage when diuretics are used for ADHF but they remain the "gold standard" therapy. Data are now emerging that diuretics drop renal blood flow and reduce GFR (Figure 19).110 Preliminary data from the Acute Decompensated Heart Failure National Registry (ADHERE)111 database have in a very provocative way suggested that significant diuretic use, especially in the setting of renal insufficiency, imparts a negative risk on survival for patients admitted with ADHF. It is advised that diuretics remain in the core treatment strategy for ADHF but judicious use ought to be considered and attention given to treatments that will minimize the need for diuretics.


tropes represent a complex treatment option. Whether catechol or non-catechol in origin, inotropes and inodilators stimulate cardiac output by upregulating cellular levels of cyclic adenosine monophosphate. Even though the increase in cardiac output is beneficial in the short term, the subsequent injury to the myocardium and the risk of serious arrhythmias mitigates against indiscriminate use of inotropes and inodilators.111 The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME) randomized 800 patients presenting with ADHF; but not in shock, to milrinone vs. placebo with background standard therapy. Milrinone was given in standard concentrations akin to its use in most medical centers. Patients receiving placebo plus standard therapy realized fewer episodes of hypotension, fewer arrhythmias, significantly fewer episodes of atrial fibrillation and a trend toward better survival (Figure 20).112 In a previous trial, which evaluated the potential benefit of prosta-cyclin in HF, a substantial number of patients received dobutamine. The short-term mortality results for these patients receiving dobutamine were quite negative. This is further supported by the adverse 6-month mortality data for patients randomized to dobutamine in the Levosimendan Infusion vs. Dobutamine (LIDO), trial,113 which evaluated the calcium sensitizer levsimendan as therapy for ADHF. Dobutamine infusions have been shown to significantly increase aldosterone levels while other catechols have been associated with striking increases in plasma renin activity.114,115 Thus, the inotropes do not represent a viable option for patients presenting with ADHF unless shock or impending shock with evidence of a low cardiac output is a significant feature of the presenting illness.116

IV nitroglycerin and nitroprusside are widely accepted as appropriate therapies for ADHF and clearly do provide transient hemodynamic improvement. Parenteral nitroglycerin is a potent peripheral and coronary vasodilator. Its greatest effect is on preload. Acute administration drops cardiac filling pressures. Sustained benefit from nitroglycerin is lacking, however, due to the rapid onset of nitrate tolerance. This greatly curtails its efficacy in the setting of ADHF117,118

Sodium nitroprusside is a balanced arterial and venodilator that drops afterload acutely and results in a reflex improvement in cardiac output. Heart rate increases with nitroprusside administration. Cyanide toxicity is an especially worrisome adverse consequence of nitroprusside use and in most facilities, the use of nitroprusside requires an intensive care unit setting, and not

<table>
<thead>
<tr>
<th>60-Day Follow-Up</th>
<th>Milrinone (n=477)</th>
<th>Control (n=472)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days until discharge</td>
<td>5.7 ± 13</td>
<td>5.9 ± 13</td>
</tr>
<tr>
<td>Adverse events</td>
<td>12.6%*</td>
<td>2.1%</td>
</tr>
<tr>
<td>Sustained hypotension</td>
<td>10.7%*</td>
<td>3.2%</td>
</tr>
<tr>
<td>Acute MI</td>
<td>1.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Rehospitalization or death</td>
<td>35.0%</td>
<td>35.3%</td>
</tr>
<tr>
<td>Death</td>
<td>10.3%</td>
<td>8.9%</td>
</tr>
</tbody>
</table>

Figure 20. Milrinone in Outcomes of a Prospective Trial of Intervention Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). Forty-eight-hour infusion of milrinone (0.5 ng/min) within 48 hours of admission for worsening of heart failure. MI=myocardial infarction; *p<0.05. Reprinted with permission from JAMA. 2002;287:1541–1547.122

Consensus Statement 10: B-Type Natriuretic Peptide as a Therapeutic Agent for Decompensated HF

10.1 The patient with ADHF has advanced disease notable for neurohormonal activation, ventricular remodeling and risk of further decompensation.

10.2 The current armamentarium of therapies and their administration for patients with ADHF have significant risks associated with their potential benefits.

10.3 IV administration of recombinant B-type natriuretic peptide (nesiritide) as a therapeutic agent has been demonstrated to maximize the risk/benefit ratio of therapies for ADHF. These benefits include hemodynamic and reverse remodeling effects while the risk of inotropy and proarrhythmia are obviated.

10.4 Because of the efficacy and utility of recombinant B-type natriuretic peptide (nesiritide) in clinical trials for patients with ADHF who are hospitalized, early data and additional trials of strategies which employ recombinant B-type natriuretic peptide (nesiritide) in either the out-patient setting or ED are currently underway.

10.5 Because of the unique homeostatic and remodeling properties of recombinant B-type natriuretic peptide (nesiritide), this therapy is also being evaluated for its role in settings such as post-MI and post-cardiac surgery.
in the construct of an effective treatment strategy for ADHF.

The complexity of the patient with ADHF is in part the reason why comprehensive guidelines have not yet been constructed. Data emanating from ADHERE have been quite revealing. The mean age of the patient admitted with ADHF is 75; nearly 50% are female and LV function is >40% in nearly half of all cases. Significant comorbidities are commonly seen, including CKD, diabetes, and atrial fibrillation. Outcomes are much less good than had been previously presumed. The risk of death during an admission for ADHF is 4% but this varies from 2% to >20% depending on the absence or presence of identified risk factors. Re-hospitalization is yet another concern with a 2% rate at 3 days, 10% at 30 days, and a 50% readmission rate at 180 days. Given the overwhelming number of annual HF admissions, now nearly 1 million, these less than ideal outcomes are especially worrisome. Clearly, better therapeutic approaches are needed.

**Natriuretic Peptides as Therapy for ADHF**. Natriuretic peptides represent a significant opportunity to reduce the morbidity of ADHF and are much closer to ideal drugs for this condition than other currently available agents.

**Hemodynamic Effects of Natriuretic Peptides**. The administration of natriuretic peptides is associated with a reduction in pulmonary capillary filling pressures, a decrease in pulmonary vascular resistance, a drop in central venous pressures, reductions in systemic BP, and a reflex increase in cardiac output due to the unloading effect of vasodilatation. What is, however, more remarkable is the lack of a reflex tachycardia, a finding consistent with the sympathoinhibitory function of natriuretic peptides (Figure 21). Moreover, the reduction in preload and afterload without an increase in heart rate would be consistent with a decrease in myocardial oxygen consumption and a decrease in ventricular stress—a stimulus that is presumed to drive the neurohormonal activation attributed to ADHF. It is also noted that tolerance to these effects has not been demonstrated, thus, these favorable changes in hemodynamics are present and persistent throughout administration of the natriuretic peptides.

**Absence of Inotropic and Proarrhythmic Effects of Natriuretic Peptides**. Classic strain-gauge physiological evaluations have clearly demonstrated that human trabeculated cardiac muscle fails to generate force-derived tension at any level of natriuretic peptide administration (Figure 22). These data plus the observed lack of reflex tachycardia support a complete absence of inotropic potential for the natriuretic peptides. The Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy (PRECEDENT) demonstrated that dobutamine increased heart rate and ventricular ectopy in a statistically significant manner compared with nesiritide. By two common criteria of pro-arrhythmia, dobutamine led to worsome ventricular arrhythmias while nesiritide did not (Figure 23). More recent data have tested the effects of B-type natriuretic peptide vs. dobutamine in patients with ADHF of ischemic etiology. There was no increase in ventricular tachycardia, couplets, repetitive beats, or resting heart rate in patients treated with nesiritide but dobutamine led to striking increases in all parameters. In fact, ventricular ectopy was decreased compared...
with baseline in those patients treated with nesiritide.\textsuperscript{135}

**Reverse Remodeling Effects of Natriuretic Peptides.** Another homeostatic attribute of B-type natriuretic peptide is the ability to restore the cardiac structure (myocyte and extracellular matrix) back toward its native state. This is perhaps the most intriguing potential benefit of the therapeutic use of natriuretic peptides. Animals devoid of NPRs demonstrate an aggressive hypertrophic response of the myocardium notable for extensive areas of fibrosis, and animals that are bred with the inability to produce B-type natriuretic peptide, demonstrate exaggerated growth responses to hemodynamic stress.\textsuperscript{136} Further, the inhibition of aldosterone and endothelin-1 contributes to a reduction in the remodeling cascade. CNP is felt to act in the central nervous system to provoke the sympathoinhibitory responses noted but may also have an anti-fibrotic role as well.\textsuperscript{137}

**Clinical Trials/Investigations Using Natriuretic Peptides as a Therapeutic Option for ADHF.** The foregoing discussion sets the stage for the use of B-type natriuretic peptides as therapy for ADHF. To date, the only available iteration of B-type natriuretic peptide is nesiritide.

Colucci et al.\textsuperscript{138} initially reported on the use of IV nesiritide as treatment of decompensated HF. Two trials were completed—the efficacy trial and the comparator trial. Patients presenting with ADHF underwent right heart catheterization followed by administration of nesiritide vs. placebo in a double blind randomized fashion. Measures of PCWP were significantly decreased and improvement in global clinical status was noted in 67% of patients on nesiritide vs. 14% on placebo. Dyspnea was reduced by 57% with nesiritide vs. 12% with placebo.\textsuperscript{138} An evaluation of the neurohormonal response to nesiritide was also completed. The reported data confirmed a significant reduction in aldosterone and a trend toward the reduction of norepinephrine in response to nesiritide administration (Figure 24).\textsuperscript{138} The conclusion was that nesiritide was “useful for the short-term treatment of decompensated HE.”

Silver et al.\textsuperscript{139} compared the effects of nesiritide vs. dobutamine on short-term outcomes in the treatment of patients with ADHE. Patients receiving nesiritide were on parenteral therapy for a statistically significant shorter period of time and trended to have fewer readmissions. Of note, the 6-month follow-up data demonstrated a lower mortality rate in patients originally treated with nesiritide compared with dobutamine (Figure 25). These data would suggest a benefit that extends beyond symptom relief and that includes a reduction in mortality vs. inotropes and a potential decrease in resource utilization for hospitalization.\textsuperscript{140}

The definitive trial was the Vasodilation in the Management of Acute CHF (VMAC) trial. This was a randomized double blind trial of 489 patients admitted with ADHF. Right heart catheterization was performed in 246 patients at the investigators’ discretion. Patients were randomized to nesiritide fixed dose or flexible dose (instrumented patients) vs. nitroglycerin, (dose adjusted per investigator), vs. placebo with background of standard therapy which included diuretics and may have included inotropes as well. The primary end point was the relief of dyspnea at 3 hours, which was achieved with nesiritide vs. placebo. At 24 hours,
the reduction in PCWP was greater for nesiritide than nitroglycerin. The conclusion was that nesiritide provided greater symptom relief and better improvement in hemodynamics than either placebo or nitroglycerin (Figure 26). Given the adverse influence of inotropes on mortality in HF, any parenteral therapy for HF must be evaluated carefully for evidence of increased mortality or other adverse risk. The totality of published data to date does not demonstrate a mortality risk of nesiritide as treatment for ADHF. Data are available from ADHERE that provide additional information on this very important topic.

Utilizing sophisticated classification and regression tree (CART) analysis statistical methodology, a comparison of outcomes within ADHERE has been completed as a function of parenteral therapies implemented. Critical to the analysis is the ability to risk adjust the data and to incorporate propensity analyses, thus accounting for adverse outcomes attributable to important comorbidities and accounting for practitioner decision making based on the absence or presence of these same comorbidities.

Within ADHERE, parenteral diuretics are utilized in 88% of all cases. Inotrope use is present in 15% of all cases and nesiritide use is now at 12% of all cases, up from 7% at the outset of ADHERE in December 2001. Risk factors for mortality in ADHERE are clustered about renal function and systolic BP. Unadjusted data that compare nesiritide to inotropes or inodilators demonstrate improved survival—a relationship that is further strengthened when the data are risk adjusted. Unadjusted data that compare nesiritide to nitroglycerin are consistent with an apparent increase in risk but once the data are adjusted for risk and propensity, there are similar outcomes seen with both nesiritide and nitroglycerin (Figure 27).

The use of nesiritide is now entering the realm of advanced HF. Patients with advanced HF, NYHA class III or IV, who are at risk for repeat hospitalization are now being evaluated as candidates for nesiritide therapy on an outpatient basis with a target of a reduction in morbidity/mortality. The recently completed Follow-up Serial Infusions of Nesiritide for HF in an Outpatient Setting (FUSION I) trial was a pilot study to test the safety of outpatient nesiritide infusions to patients.
with advanced HF. Patients already demonstrated to have advanced HF and a history of recent hospitalizations were randomized to one of three arms: usual care; weekly nesiritide infusions at 0.005 µg/kg/min plus usual care; and weekly nesiritide infusions at 0.01 µg/kg/min plus usual care. In this open label randomized trial of 210 patients, nesiritide therapy was surprisingly well tolerated. Fewer than 1% of the >1600 infusions administered during the trial had to be stopped for adverse events.

In a prospectively identified group of patients deemed to be at high risk based on the presence of four or more known risk factors, there was a signal of clinical efficacy with an improvement in days alive and out of hospital (Figure 28). A larger 900 patient double blind randomized placebo controlled trial, FUSION II, is now underway.

Future directions for therapeutic uses of nesiritide include: post-MI to effect a decrease in LV remodeling; post-cardiopulmonary bypass to mitigate postoperative renal insufficiency and to improve cardiac outcomes; pre-heart transplantation as a bridge to transplant; and a chronic ambulatory HF initiative utilizing subcutaneously administered B-type natriuretic peptide as adjunctive therapy to chronic evidence-based HF management.

**Therapeutic Summary.** This rapidly evolving spectrum of therapeutic benefit and the emerging realm of additional therapeutic potential positions B-type natriuretic peptide as an increasingly important treatment option in the management of a growing number of cardiovascular conditions. The current approved use of nesiritide is for decompensated HF. Although guideline statements for ADHF are lacking, the totality of diagnostic and therapeutic data regarding natriuretic peptides yields an intuitively rational and reasonably evidence-based approach for the assessment and management of ADHF. A practical and clinically useful decision-making framework is suggested in Figure 29 as an adaptation of an algorithm developed by Maisel.

### Additional Considerations

**Implications of BNP Levels in the Outpatient Management of HF.** Elevations of BNP have been shown to be a powerful marker for prognosis and risk stratification in the setting of HF. In a recent study of 78 patients referred to an HF clinic, BNP showed a significant correlation to the HF survival score. In addition, changes in plasma BNP levels were significantly related to changes in limitations of physical activities and were a powerful predictor of functional status deterioration.

REDHOT demonstrated a “disconnect” between the perceived severity of HF cases by ED physicians and severity as determined by BNP levels. Therefore, an algorithm utilizing BNP may better determine severity of congestive HF than clinical judgment alone.

### Analysis

<table>
<thead>
<tr>
<th></th>
<th>Nesiritide vs. NTG</th>
<th>Nesiritide vs. milrinone</th>
<th>Nesiritide vs. dobutamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.62*</td>
<td>0.53*</td>
<td>0.36*</td>
</tr>
<tr>
<td>Adjusted for covariates, sex, age, BUN, SBP, DBP, CR</td>
<td>0.85§</td>
<td>0.58*</td>
<td>0.51*</td>
</tr>
<tr>
<td>Adjusted for covariates and propensity score</td>
<td>0.83†</td>
<td>0.57*</td>
<td>0.41*</td>
</tr>
</tbody>
</table>

Nesiritide n=2128; NTG n=3457; milrinone n=1205; dobutamine n=2211

Figure 27. Effects of IV vasoactive medications on mortality in the Acute Decompensated Heart Failure National Registry (ADHERE). NTG=nitroglycerin; BUN=blood urea nitrogen; SBP=systolic blood pressure; DBP=diastolic blood pressure; CR=creatinine; *p<0.0002; †p=0.24; ‡p=0.19.


ADHERE registry is the largest registry for decompensated HF, currently enrolling about 100,000 patients (Figures 30, 31). One of the most impressive findings thus far is the notion that beginning vasoactive therapy in the ED was associated with a 3.1-day reduction in hospital length of stay compared with when such therapies were not initiated until after admission. This analysis suggests that choice of therapy in the ED may critically impact the course of patients with HF.

The Prospective Randomized Outcomes Study of Acutely Decompensated HF Treated Initially in Outpatients with Natrecor (PROACTION) emergency medicine pilot trial of patients with acute HF randomized in the ED showed a potential benefit of using nesiritide along with standard therapy. While the
BNP Consensus Panel 2004  

Figure 29. The evaluation and treatment of patients presenting with acute dyspnea. HF=heart failure; BP=blood pressure; ECG=electrocardiogram; BNP=B-type natriuretic peptide; COPD=chronic obstructive pulmonary disease; BUN=blood urea nitrogen; Creat=creatinine; CrCl=creatinine clearance; CKD=chronic kidney disease. ©MedReviews, LLC. Reprinted with permission of MedReviews, LLC. Maisel A. B-type natriuretic peptide measurements in diagnosing congestive heart failure. Rev Cardiovasc Med. 2002;3(suppl 4):S10–S17. Reviews in Cardiovascular Medicine is a copyrighted publication of MedReviews, LLC. All rights reserved.

Figure 30. Relationship of hospital length of stay (days) and site of initiation of vasoactive therapies. ED=emergency department. Reprinted with permission from Ann Emerg Med. 2003;42(4):S26.


Figure 29. The evaluation and treatment of patients presenting with acute dyspnea. HF=heart failure; BP=blood pressure; ECG=electrocardiogram; BNP=B-type natriuretic peptide; COPD=chronic obstructive pulmonary disease; BUN=blood urea nitrogen; Creat=creatinine; CrCl=creatinine clearance; CKD=chronic kidney disease. ©MedReviews, LLC. Reprinted with permission of MedReviews, LLC. Maisel A. B-type natriuretic peptide measurements in diagnosing congestive heart failure. Rev Cardiovasc Med. 2002;3(suppl 4):S10–S17. Reviews in Cardiovascular Medicine is a copyrighted publication of MedReviews, LLC. All rights reserved.

Figure 30. Relationship of hospital length of stay (days) and site of initiation of vasoactive therapies. ED=emergency department. Reprinted with permission from Ann Emerg Med. 2003;42(4):S26.


length of stay was the same for the two cohorts, in the subsequent 30 days, patients receiving nesiritide spent clinically important and statistically signifi-cantly fewer hospital days compared with standard care (2.5 vs. 6.5 days) over the next month.

Integrating BNP Levels Into a Rational Use of Nesiritide. While BNP is approved by the FDA for the diagnosis of HF, its usefulness to monitor effective-ness in treatment is still under study. However, as it appears that many hos-pitals and clinics are already using BNP levels to guide therapy, some suggestions can be made. One can stratify patients to the high-risk category in part using BNP levels. Fonarow’s group148 found three independent predictors of acute mortality at the index admission, derived from >80,000 patients in the ADHERE registry. They are a blood urea nitrogen >43 mg/dL, systolic BP <115 mm Hg, or a creatinine >2.75 mg/dL. Since these are each independently associated with death at the current hospitalization, the presence of any one suggests the need for aggressive therapy. Furthermore, these indicators are additive; if none are present, index visit mortality is 2.2%, compared with >22% if all three occur.

If patients are admitted with BNP levels <600 pg/mL and blood urea nitrogen levels are <40 (i.e., lower risk), one can often start with parenteral diuretics. Subsequently, the patient can be reclassified into low- or high-risk groups based on their response over the next 6–12 hours. Patients who have an adequate diuresis, a fall in BNP level, and no deterioration in renal function might opt for continued diuretics/vasodilators until euvolemia is reached. Hopefully, this will lead to a BNP <400 pg/mL. In one study, patients whose discharge BNP levels fell below 430 pg/mL had a reasonable likelihood of not being readmitted within the following 30 days.66 If the BNP level is higher than this, the patient’s volume status should be reevaluated. If it is determined that the patient is not yet euvolemic, nesiritide might be considered for 24–48 hours.

After receiving short-term parenter-al diuretics, patients with an inadequate diuresis, no change, or an increase in BNP level, and worsening renal func-tion, should be considered to be high risk. If these patients have a systolic BP of at least 90 mm Hg, they can be given 24–48 hours of nesiritide therapy along with IV diuretics. BNP levels can then be checked several hours after cessation of nesiritide. IV or oral diuretics and vasodilators can then be used until euvolemia is achieved.

Patients with systolic BPs <90 mm Hg often need vasopressors and/or inotropes, sometimes under Swan-Ganz catheter monitoring guidance. In our experience, if these patients show improvement in BP and symptoms, they can then be transitioned to nesiritide. If there is no improvement on inotropes or pressors, further invasive strategies need to be consid-ered. Finally, it is conceivable that in patients who are admitted with very high BNP levels and impaired renal function, nesiritide could be started immediately.

Toward the Future: Monitoring BNP Levels Post-Hospitalization—Implications for BNP-Guided Outpatient Treatment. Perhaps an important marker for rehospitalization risk is a post-discharge rise in BNP. Early after discharge, rise in BNP levels often are associated with volume overload and diuretics may need to be adjusted. As is the practice at several institutions,149 when a patient with HF comes to the urgent care center with symptoms that could represent a decompensated state,
A BNP level is drawn. If no different from baseline values, then decompensation is unlikely. How high a BNP should be over baseline to call it decompensated is not known. As BNP should not be used without clinical context, it should be used in conjunction with other features of the history and physical exam (clinical features of decompensation along with an increase of 50% or more from baseline are often associated with decompensation in the patient’s experience).

The correlation between the drop in BNP level and the patient’s improvement in symptoms (and subsequent outcome) during hospitalization suggests that BNP-guided treatment might make “tailored therapy” more effective in an outpatient setting such as a primary care or cardiology clinic. The Australia-New Zealand HF Group analyzed plasma neurohormones for prediction of adverse outcomes and response to treatment in 415 patients with LV dysfunction, randomly assigned to receive carvedilol or placebo. They found that BNP was the best prognostic predictor of success or failure of carvedilol use. Recently, Troughton et al. randomized 69 patients to NT-BNP–guided treatment vs. symptom-guided therapy. Patients receiving NT-BNP–guided therapy had lower NT-BNP levels along with reduced incidence of cardiovascular death, readmission, and new episodes of decompensated HF. This study has spawned a number of larger studies including the multicenter Rapid Assessment of Bedside BNP In Treatment of HF (RABBIT) trial. It is evident that patients with poor ejection fraction but with BNP levels that are <200 pg/mL have a very good prognosis. A study of 452 ambulatory patients with an LV ejection fraction <35% found that in patients with mild-to-moderate HF (NYHA functional class II/III), BNP levels were independent predictors of sudden death, an important cause of mortality in these patients. They found that a cutoff BNP level of 130 pg/mL differentiated between patients with high and low survival rates of sudden death. Only 1% (1 of 110) of those patients with BNP levels below the cutoff point died suddenly; in comparison to a sudden death rate of 19% (43 of 227) among those patients with BNP levels above the cutoff point.

Using BNP levels to identify a patient population with a higher risk of sudden death can help to tailor their treatment and extend survival.

It also appears that angiotensin converting enzyme inhibitors, angiotensin-receptor blocker agents, aldosterone antagonists, and perhaps β blockers drive BNP levels down, although it is unclear whether this is a true marker of clinical improvement. In Val-HeFT, changes in BNP over time induced by pharmacologic therapy were shown for the first time to correlate with morbidity and mortality. Patients with the greatest percentage decrease in BNP and norepinephrine from baseline had the lowest morbidity and mortality, whereas patients with the greatest percentage increase in BNP and norepinephrine were at the greatest risk. The authors found BNP to be more predictive of morbidity and mortality than norepinephrine or, in a separate analysis, than aldosterone.

The current practice of some physicians is to aim for BNP levels <200–300 pg/mL with standard therapy of angiotensin-converting enzyme inhibitors and β blockers and diuretics. Patients with BNP levels between 200 and 500 pg/mL are often NYHA functional class II/III and may require more diuretics, especially spironolactone. Patients who, despite standard medical treatment, have advanced symptoms along with high BNP levels (400–600 pg/mL) might be candidates for continuous and palliative outpatient infusions of inotropes or nesiritide, biventricular pacing (if QRS >120–130 ms), cardiac transplantation, or LV assist device. In the future stem cell or gene therapy may have a role in treatment of these patients.

**Conclusions**

The data presented and reviewed above are likely to represent a small percentage of our knowledge about the natriuretic peptide system as it unfolds in the months and years ahead. Nonetheless, it is clear that this important homeostatic system impacts so specifically the cardiovascular system that all interested in heart and blood vessel disease must remain cognizant of the advances in this discipline. The Panel hopes we have contributed to the current understanding of this area.

We hope that after reading this document you have a heightened interest and understanding of the importance and ramifications of the natriuretic peptide system. We will continue to follow the developments in this area and update this consensus as new research becomes available.

The Consensus Statements are available in pocket accordion format. For copies please contact your local representative from:

Abbott Laboratories Diagnostics Division, Bayer HealthCare Diagnostics Division, Biosite, or SCIOS.
REFERENCES

1. Data on file at Biosite, Inc.
57 Sengenes C, Berlan M, De Glisezinski I, et al. Natriuretic peptides: a new lipo-
59 McCord J, Mundy BJ, Hudson MP, et al. For the BNP Multinational Study Investi-
61 Koglin J, Pehlivanli S, Schwaiblmaier M, et al. Role of brain natriuretic peptide in risk strati-
67 O’Leary DM, Durr J, Jourdain P, et al. Cost-effectiveness of screening with Cardiac troponin I as diagnostic and prog-
68 Silver MA, Pisa SA, Levy D, et al. Plasma natriuretic peptide levels and the risk of car-
71 Aronson D, Burger AJ. Intravenous nesiritide for acute heart failure without normalization of brain natri-
74 Pitt B, Remme W, Zannad F, et al. Transforming growth factor-beta 1 hypere-
of excessive extracellular matrix turnover may contribute to survival benefit of sphino-
lactone therapy in patients with congestive heart failure: insights from the Randomized
Alldosterone Evaluation Study. (RALES).
111 Kirchgeister M, Munter K. Endothelin-1 and endothelin receptor antagonists in cardio-
vascular remodeling, mini review. P.S.E.B.M.
1999;221:312–325.
112 de Bold AJ, Borenstein HB, Veress AT, et al. A rapid and potent natriuretic response to intra-
113 Mukoyama M, Nakao K, Haisuda N, et al. Brain natriuretic peptide as a novel cardiac hor-
mon neurotransmitter in humans: evidence for an exquisite dual natriuretic peptide system, atrial natri-
114 Koller K, Goeddel D. Molecular biology of the group C natriuretic peptides and their receptors.
117 Kudo T, Baird A. Inhibition of aldosterone produc-
tion in the adrenal glanduromas by atrial natri-
119 Gottlieb SS, Brater DC, Thomas I, et al. BNP9719 (CVT-124), an A1 adenosine recep-
120 Costanzo MR, Heywood JT, DeMarco, et al. Impact of renal insufficiency and chronic diuretic therapy on outcome and resource utilization in patients with acute decompens-
ated heart failure. Presented at the American College of Cardiology, March 2004, New Orleans, LA.
122 Colby AV, Califf RM, Adams KF, et al. Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIM-ECHF) Investigators: Short-term intravenous milr-
inone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA.
123 Follath F, Cleland JG, Just H, et al., for the Steering Committee and Investigators of the Levosimendon infusion versus Dobutamine (LIDO) Study. Efficacy and safety of intravenous levo-
simendon compared with dobuta-
124 Aronson D, Horton DP, Burger AJ. The effect of dobutamine on neuronal and cyto-
125 Watten CG, Mackay KS, Glover DR, et al. Effect of the partial beta-agonist pre-
127 Elakayum U, Roth A, Henriquez B, et al. Hemodynamic and hormonal effects of high-
129 Feinberg A, Bettencourt P, Dias P, et al. Neurohemoral activation, the renal dopami-
132 Butler J, Emerman C, Peacock WF, et al., on behalf of the VMAC study investigators. The
Comparison of in-hospital mortality in patients treated with nesiritide versus other parenteral vasoactive medications for acutely decompens-
135 Chen HH, Grantham JA, Schirger JA, et al. Subcutaneous administration of brain natri-
136 Koglin J, Pehlivanli S, Schwaabmlir M, et al. Role of brain natriuretic peptide in risk stratifi-
138 Fonarow GC, Abraham WT, Adam K. Risk stratifi-
cation from inhospital mortality in heart failure using classification and regression tree (CART) methodology: analysis of 33,046 patients in ADHERE Circulation. 2003;108:IV–693.

30 BNP Consensus Panel 2004

September - October 2004 - Supplement 3