Natriuretic peptides in the diagnosis and management of heart failure

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ABSTRACT

The natriuretic peptides are a family of related hormones that play a crucial role in cardiovascular homeostasis. They have recently emerged as potentially important clinical markers in heart failure. Recent data have suggested an important role for these markers in establishing the diagnosis of heart failure in patients with unexplained dyspnea in both acute care and ambulatory settings. Other clinical uses of the natriuretic peptides, such as screening for asymptomatic ventricular dysfunction, establishing prognosis or guiding titration of drug therapy, are under investigation but have not yet sufficiently been validated for widespread clinical use.

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Physiology of natriuretic peptides

BNP and ANP are synthesized in myocytes as larger molecules (e.g., proBNP) that are subsequently cleaved to yield the active peptide hormone (e.g., BNP) and the biologically inactive N-terminal peptide fragment (e.g., NT-proBNP). Both ANP and BNP activate the same transmembrane receptor (natriuretic peptide receptor A) on target organs and as a consequence have similar physiologic effects — both hormones promote the renal excretion of sodium (natriuresis) and water (diuresis), cause vasodilation by relaxing vascular smooth muscle cells, improve diastolic relaxation (lusitropy) and decrease myocardial fibrosis. ANP and BNP do differ in their physiologic regulation, with ANP acting as the primary circulating natriuretic peptide hormone under normal conditions and BNP secretion being primarily as a result of increased myocardial wall stress. The normal circulating level of BNP is less than 20% that of ANP, but BNP is rapidly secreted by the ventricles in response to hemodynamic stress.4

ANP and BNP are removed from the circulation by 2 pathways: receptor-mediated internalization and metabolism (primarily in the kidneys), and proteolytic degradation by neutral endopeptidase in the kidneys, vascular endothelium, lungs and heart. BNP has slower clearance than ANP by both pathways. Consequently, the circulating half-life of ANP is 3–5 minutes, whereas the half-life of BNP is about 23 minutes. The inactive terminal fragment NT-proBNP has an even greater half-life than that of BNP (60–120 minutes), which is relevant to its value as a diagnostic test.

The path that connects the discovery of the natriuretic peptides with their current clinical roles begins over 50 years ago, when electron microscopy studies identified secretory granules in atrial muscle cells. In 1961, de Bold and colleagues from Ottawa found that injection of atrial muscle cell extracts into rats produced a marked increase in sodium and water excretion and a drop in blood pressure.3 This “atrial natriuretic factor” was the first demonstration of an endocrine function for the heart. The structure of the responsible peptide hormone — atrial (now termed A-type) natriuretic peptide or ANP — was reported in 1983 by de Bold’s group and in 1984 by Kangawa and Matsuo in Japan. Subsequent studies identified 2 more related peptides — brain (now termed B-type) natriuretic peptide or BNP, and C-type natriuretic peptide or CNP (which appears to act primarily in the peripheral vasculature and will not be discussed further in this review). When research laboratory assays became available for ANP and BNP in the 1990s, investigators were able to demonstrate that the levels of these hormones varied according to the presence and severity of heart failure. Most of the evidence supporting the clinical use of natriuretic peptide testing in heart failure has been published since 2000.

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Historical perspective

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Comparisons of the diagnostic performance of ANP and BNP have generally favoured BNP. Thus, most of the clinical work developing natriuretic peptides as diagnostic tests has focused on BNP or NT-proBNP, and we will focus on the use of these molecules in this review.

**Measurement of BNP and defining normal values**

Laboratory-based assays and point-of-care assays are available for BNP and NT-proBNP using fully automated immunoassays. The most commonly used decision threshold for BNP is 100 pg/mL; the corresponding values for NT-proBNP are 125 pg/mL for patients less than 75 years old and 450 pg/mL for those 75 or older. Different commercial assays for BNP do not give interchangeable results, and therefore the assay being used must be noted when interpreting clinical test results as well as results from published studies. Available data suggest that the BNP and NT-proBNP have similar accuracy in the diagnosis of acute dyspnea.

Levels of both molecules are elevated with aging and are higher in women than in men. A useful rule of thumb is that the BNP level in a normal person should be less than half their chronologic age. Obesity has also recently emerged as another possible confounder of natriuretic peptide measurement, with lower natriuretic peptide levels observed with progressively higher body mass index (BMI). Among 746 apparently healthy subjects in one study, however, BMI had no effect on NT-proBNP levels after adjusting for age and sex.

In the Dallas Heart Study, both BNP and NT-proBNP levels were associated more strongly with greater lean rather than fat mass. Some investigators have suggested that lower levels of natriuretic peptides observed in obese patients may contribute to the association between obesity and hypertension and related disorders. Renal insufficiency affects the levels of both BNP and NT-proBNP. In one large registry study, BNP had a modest correlation with renal function, and levels were increased in patients with a creatinine clearance of less than 60 mL·min⁻¹·1.73 m⁻². The investigators proposed that the reference value for these patients should be 200 pg/mL. A similar NT-proBNP study found a moderately strong inverse relation with renal function, and the authors recommended a reference value of 1200 pg/mL for patients with an estimated creatinine clearance below 60 mL·min⁻¹·1.73 m⁻².

In addition to the factors discussed above, BNP levels may be altered by co-existing cardiovascular diseases and by non-cardiovascular diseases (Box 1). In the remainder of this review, we will use BNP as a general term and specify BNP or NT-proBNP when discussing specific studies (Table 1).

| Box 1: Potential causes of elevated B-type natriuretic peptide levels |
|---------------------------------------------------------------|
| **Cardiac** |
| • Heart failure |
| • Diastolic dysfunction |
| • Acute coronary syndromes |
| • Hypertension with left ventricular hypertrophy |
| • Valvular heart disease (aortic stenosis, mitral valve regurgitation) |
| • Atrial fibrillation |
| 
| **Noncardiac** |
| • Acute pulmonary embolism |
| • Pulmonary hypertension (primary or secondary) |
| • Sepsis (possibly due to tissue hypoxia or secondary myocardial depression) |
| • Chronic obstructive pulmonary disease with cor pulmonale or respiratory failure |
| • Hyperthyroidism |

**Diagnostic use of BNP testing in the evaluation of acute dyspnea**

Four major applications of BNP testing in heart failure patients have emerged over the last decade (Table 2). Because the diagnosis of heart failure is often challenging, the possibility that a serologic test might provide either simplification or improved accuracy has great appeal.

Methodologic challenges in interpreting the literature on the diagnostic uses of BNP derive from 3 sources. First, many investigations empirically derive a new BNP positive/negative cut point in each new dataset without then validating the performance of this cut point in an independent dataset. This practice makes comparison across studies difficult and, without validation, the reader should be skeptical that the test will be as accurate in routine clinical practice. Second, many studies are small, single-centre investigations that cannot offer robust guidance on the clinical utility of these tests. Finally, many reports on the diagnostic use of BNP testing in heart failure present the negative predictive value of the test as if it were another measure of test performance, such as sensitivity and specificity. The negative predictive value, however, is simply the post-test probability of disease following a negative test result.

| Table 1: Characteristics of B-type natriuretic peptide (BNP) and N-terminal BNP fragment (NT-proBNP) |
|---------------------------------------------------------------|
| **Characteristic** | BNP | NT-proBNP |
| Size, no. of amino acids | 32 | 76 |
| Activity | Bioactive | Inactive |
| Normal plasma concentration, pg/mL | 5–50 | 7–160 |
| Half-life in plasma, min | –22 | –60–120 |
| Time to reflect meaningful hemodynamic changes, h | –2 | –12 |
| Approved cutoff to define abnormal range, pg/mL | 100 | 125 (< 75 yr) |
| | | 450 (≥ 75 yr) |

Modified, with permission, from Rademaker and Richards. © Biochemical Society. *As defined by package insert for Biosite (BNP) and Roche Diagnostics (NT-proBNP) assays.
result. Consequently, it varies as a function of both disease prevalence (pre-test probability) and test accuracy (sensitivity and specificity), as specified in Bayes’ Theorem. Reporting of the post-test probability of acute heart failure in the same population in which sensitivity and specificity were measured is of little practical use to clinicians who will often need to make decisions regarding the management of patients with different pre-test probabilities of disease. Thus, the important parameters to examine in this literature include the prevalence of disease in the tested population and the estimated accuracy parameters, which can be usefully summarized as the likelihood ratios for a positive and negative test.

The strongest evidence for the use of BNP testing is in the evaluation of heart failure as a cause of acute dyspnea in the emergency department. Wang and colleagues recently published a meta-analysis examining the value of BNP measurement in this setting. Studies involving ANP or NT-proBNP alone were excluded. These investigators identified 11 studies published between 1994 and July 2005 and judged 7 to be in the top 2 tiers of quality owing to prospective design, use of consecutive or random patients and use of 2 or more blinded raters to establish the diagnosis of heart failure. These 11 studies employed 5 different binary cut points to establish a “positive” BNP test result, ranging from 50 pg/mL to 250 pg/mL. As expected, with lower threshold values for a positive test result, sensitivity improved while specificity declined substantially. An elevated BNP, however defined, raised the likelihood of heart failure as the correct diagnosis by about 2–4.5 times, whereas a value below 250 pg/mL decreased the likelihood of heart failure by about 90%. In contrast, a subjective assessment by an emergency physician of a high clinical pre-test probability (≥ 80%) increased the likelihood of heart failure by 10 times, whereas a low pre-test probability (≤ 20%) as assessed by an emergency physician reduced the post-test probability of heart failure by 35%.

The largest study to evaluate the role of BNP in the diagnosis of acute dyspnea was the Breathing Not Properly (BNP) Multinational Study, a prospective multicentre registry of 1586 patients. Results of BNP assays were not available to the treating physicians, and a final diagnosis for each patient was adjudicated by a panel of cardiologists (who were also blinded to the BNP results). The prevalence of heart failure in this population was 47%. BNP levels were significantly greater (mean BNP 675 pg/mL) among patients with a final diagnosis of heart failure than among those with left ventricular dysfunction but another cause of dyspnea (mean BNP 346 pg/mL) or no left ventricular dysfunction or heart failure (mean BNP 110 pg/mL). A BNP cutoff of 100 pg/mL was selected for clinical use (sensitivity 90%, specificity 76%).

The ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study used a design similar to the BNP Study to evaluate the utility of NT-proBNP in the emergency department evaluation of 600 dyspnea patients presenting to a single Boston medical centre. The prevalence of acute heart failure in this cohort was 35%. A decision level of less than 450 pg/mL had a sensitivity of 98% and specificity of 76% (Fig. 1). As in the BNP Study, the use in PRIDE of the emergency physician’s initial clinical assessment together with NT-proBNP was superior to either factor alone and gave the best combination of sensitivity and specificity. Clinical and BNP

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**Table 2: Major applications of BNP testing in heart failure patients**

| Indication; study | Marker | Clinical setting | Comment |
|------------------|--------|------------------|---------|
| **Diagnosis**    |        |                  |         |
| Maisel et al20   | BNP    | ED patients with acute dyspnea | Level of 100 pg/mL identified as optimal cutoff for diagnosis of heart failure |
| Januzzi et al21  | NT-proBNP | ED patients with acute dyspnea | Level > 450 pg/mL in patients aged < 50 yr and > 900 pg/mL in patients ≥ 50 yr identified as optimal cutoff for diagnosis; subsequently validated in independent dataset22 |
| Cowie et al21    | BNP    | Primary care clinic | Level of 76 pg/mL identified as optimal cutoff for diagnosis of heart failure |
| **Screening**    |        |                  |         |
| Vasan et al24    | BNP    | Observational cohort study | Area under ROC curve < 0.75 for detecting asymptomatic left ventricular dysfunction, which suggests poor performance as screening test |
| Redfield et al25  | BNP    | Observational cohort study | Area under ROC curve < 0.75 for identifying subclinical diastolic dysfunction, which suggests poor performance as a screening test |
| **Prognosis**    |        |                  |         |
| Anand et al26    | BNP    | Clinical trial of valsartan | Level > 97 pg/mL associated with doubling of long-term morbidity and mortality (relative risk 2.1) |
| **Guiding therapy** |       |                  |         |
| Troughton et al27| NT-proBNP | Randomized clinical trial | Therapy guided by NT-proBNP levels associated with significant decrease in composite of heart failure, hospital admission or death |

Note: BNP = B-type natriuretic peptide, ED = emergency department, NT-proBNP = N-terminal BNP fragment, ROC = receiver operating characteristic.
data were formed into an 8-item diagnostic heart failure score using logistic regression analysis (Table 3), and the score was then externally validated in an independent study cohort from New Zealand. As shown in Fig. 2, the score showed a strong linear association with the diagnosis of acute heart failure.

As with other diagnostic tests, BNP has the greatest chance to change management when it is measured in patients in whom there is the most diagnostic uncertainty. Based on simple Bayes’ Theorem considerations, in patients with pretest probabilities of about 50%, a likelihood ratio for a positive test (sensitivity/(1 – specificity)), or the ratio of true positives to false positives) of about 10 is needed to raise diagnostic certainty after testing to 90% or more (see Fig. 3). In the meta-analysis of Wang and colleagues, a high clinical index of suspicion for heart failure had a likelihood ratio of about 10, whereas a “positive” BNP had a likelihood ratio of 3 to 4. Of note, the likelihood ratio for either a high clinical suspicion or a BNP level of 100 pg/mL or greater was 3.1, which was not a significant improvement over BNP alone. In contrast, Wang and colleagues calculated a likelihood ratio for a “negative” BNP ((1 – sensitivity)/specificity, or the ratio of false negatives to true negatives) of 0.11, which would move patients in whom there is diagnostic uncertainty to a post-test probability of 10% or less.

One important but infrequently discussed issue is how low the post-test probability of heart failure needs to be for the clinician to be able to make confident management decisions. If the post-test probability of heart failure after a negative BNP test result is about 10%, as shown in Fig. 3, then 10 of every 100 such patients who are sent home with reassurance and nonspecific therapy will, in fact, have acute heart failure. Whether this is an acceptable error rate depends on the consequences of failing to admit and treat the patient in a timely fashion, an issue that has not been adequately examined. If the clinician requires a higher level of certainty before deciding to discharge a patient from the emergency department (e.g., post-test probability ≤ 5%), a negative BNP test result will only provide this if the pre-test probability is less than or equal to about 35% (i.e., lower than in either the BNP Multinational Study or the PRIDE Study).

Based on these considerations, the BNP and NT-proBNP are most useful in patients presenting to the emergency department with acute dyspnea with a low to intermediate pre-test probability if the test results are negative according to conventional decision levels. If the clinician’s pre-test probability of heart failure as the cause of the patient’s dyspnea is high, a negative BNP test result should not, by itself, be used to dismiss the diagnosis.

### Diagnostic uses of BNP in the nonacute setting

#### Heart failure

The possibility that BNP testing might be of use in the diagnosis of heart failure in the primary care setting was first examined by Cowie and colleagues. They studied 122 consecutive patients who were referred by their general practitioner to a heart failure clinic in west London over a 15-month pe-

| Cutoff, pg/mL | Sensitivity, % | Specificity, % | PPV, % | NPV, % | Accuracy, % |
|--------------|---------------|----------------|--------|--------|-------------|
| 300          | 99            | 68             | 62     | 99     | 79          |
| 450          | 98            | 76             | 68     | 99     | 83          |
| 600          | 96            | 81             | 73     | 97     | 86          |
| 900          | 90            | 85             | 76     | 94     | 87          |
| 1000         | 87            | 86             | 78     | 91     | 87          |

Note: PPV = positive predictive value, NPV = negative predictive value.

#### Table 3: Components of diagnostic score used in the PRIDE study

| Component                          | Points |
|------------------------------------|--------|
| Elevated NT-proBNP level > 450 pg/mL if age < 50 yr | 4      |
| > 900 pg/mL if age ≥ 50 yr          |        |
| Interstitial edema on chest radiograph | 2      |
| Orthopnea                          | 2      |
| Absence of fever                   | 2      |
| Current loop diuretic use          | 1      |
| Age > 75 yr                        | 1      |
| Rales on lung examination          | 1      |
| Lack of cough                      | 1      |
| Total score                        | 0.14   |

Note: PRIDE = ProBNP Investigation of Dyspnea in the Emergency Department, BNP = B-type natriuretic peptide, NT-proBNP = N-terminal BNP fragment.

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Fig. 1: Receiver operating characteristic (ROC) curve for N-terminal B-type natriuretic peptide fragment (NT-proBNP) in the PRIDE study involving 600 patients presenting to the emergency department with acute dyspnea. Five possible decision thresholds are shown, ranging from 300 to 1000 pg/mL, with corresponding sensitivities and specificities. Reproduced, with permission, from Januzzi et al. Additional data provided by Januzzi.
The median interval between initial evaluation and referral was 4 days. The “gold standard” diagnosis of heart failure was made by a panel of 3 cardiologists using retrospective record review. In this early study, no formal quantification of pretest probability was made. For a BNP level of 76 pg/mL (22 pmol/L) or greater, the authors calculated a sensitivity of 97% and specificity of 84%. The corresponding likelihood ratios for a positive and negative test result are 6.1 and 0.04. Thus, greater diagnostic certainty is again provided for patients who, on clinical evaluation, have a low to intermediate pretest probability of heart failure together with a negative BNP test result.

In a randomized trial that enrolled 305 elderly outpatients with symptoms of dyspnea or edema of recent onset, general practitioners became more accurate in their diagnosis of heart failure with the addition of NT-proBNP results to the standard clinical assessment (70% correct diagnosis with BNP results v. 59% without BNP results). Most of the improved accuracy was due to enhanced correct elimination of the diagnosis of heart failure as the cause of symptoms.

Left ventricular dysfunction

Two groups of investigators have performed systematic reviews on the diagnostic uses of BNP measurement in heart failure. Latour-Perez and colleagues identified 25 studies of adequate quality examining the ability of BNP to identify systolic dysfunction. The studies were clinically heterogeneous in the types of patients studied, in the BNP cut points used and in the definition of systolic dysfunction. The summary diagnostic odds ratio showed strong evidence of statistical heterogeneity and evidence of publication bias.

A recent representative study involved a randomly selected population of Olmstead County residents over 45 years old who underwent echocardiography and BNP testing. Using the empirically derived BNP cutoff of 55 pg/mL for the identification of preclinical systolic dysfunction (ejection fraction ≤ 40%, which had a prevalence of 1%), the authors found that a positive BNP test result had a likelihood ratio of 3.8, whereas a negative result had a likelihood ratio of 0.1. In this population, using BNP measurement as an initial screen would lead to a referral for echocardiography in 24% of the patients. In 96% of these studies, the results would be negative for systolic dysfunction. Comparable results were reported in the Framingham Offspring Study. For detection of moderate or severe diastolic dysfunction, the situation is even less favourable. Use of an empirically derived cut point of 36 pg/mL yielded a positive likelihood ratio of 2.4 and a negative likelihood ratio of 0.4. A “positive” BNP would lead to 34% of patients being referred for echocardiography, of whom 85% would have negative findings. Taken as a whole, these data suggest that the use of natriuretic peptides for screening asymptomatic populations is not likely to be cost-effective.
Prognostic uses of BNP in heart failure

Doust and colleagues identified 19 studies examining the prognostic value of BNP or NT-proBNP in heart failure.\textsuperscript{35} These studies were published between 1994 and March 2004 and differed in how they analyzed BNP (as a continuous variable v. dichotomized into groups) and whether they examined survival alone or combined cardiac events (typically death or hospital admission). Pooled analysis of 4 studies that used continuous BNP to predict all-cause mortality indicated that, for each 100 pg/mL rise in BNP, the relative risk of death increased by 35%. The studies using a dichotomous BNP were more variable. The largest of these, theValsartan Heart Failure Trial (Val-HeFT) using a subset of 3618 patients, reported a doubling of mortality among patients with a BNP level greater than 97 pg/mL.\textsuperscript{36} Although these data support the strong prognostic value of natriuretic peptide levels, it should be noted that this literature is particularly susceptible to publication bias (i.e., studies that found weak or no association between BNP and prognosis are less likely to be published).

Logeart and colleagues examined the prognostic value of serial admission and discharge BNP measurements among 105 patients surviving hospital stay for decompensated heart failure and discharged with either New York Heart Association (NYHA) class II or III disease.\textsuperscript{37} The predischarge BNP was the strongest predictor of death or readmission because of heart failure, whereas admission BNP, and clinical and echocardiography parameters did not add independent information. A BNP level of 350 pg/mL was selected as the best cutoff for clinical use. In a subsequent validation cohort of 109 patients, the use of this BNP cutoff had a sensitivity of 80% and a specificity of 88% for identifying subsequent death or hospital admission at 6 months. Similar results have recently been reported by Verdiani and coworkers.\textsuperscript{38}

Monitoring response to heart failure therapy with BNP

The case for BNP-guided therapy depends on several important assumptions. The first, for which there is reasonable evidence, is that therapies that reduce adverse clinical events in heart failure also reduce BNP levels. BNP levels have improved with a variety of drug therapies known to be efficacious in heart failure, including angiotensin-converting-enzyme (ACE) inhibitors,\textsuperscript{39} angiotensin-receptor blockers,\textsuperscript{40} β-blockers\textsuperscript{41} and spironolactone.\textsuperscript{42} The second assumption, for which there is much less evidence, is that therapies that improve outcomes in heart failure do so primarily through mechanisms that are linked with changes in BNP levels. In an early study involving 20 patients with decompensated heart failure, changes in BNP levels mirrored changes in pulmonary wedge pressures.\textsuperscript{43} However, repeated evidence in medicine that surrogate end points often do not behave as expected highlights the necessity of demonstrating in large studies the connection between changes in BNP and patient outcomes.

Finally, the concept of BNP-guided therapy presumes that BNP data will direct the clinician to make changes in therapy that would not otherwise be made. For most of heart failure therapy, however, drug dosage is based on patient tolerance and the targets achieved in the pivotal clinical trials, not on response to therapy.\textsuperscript{44} Only in the case of diuretic dose is there a major opportunity to alter management by providing additional information about the patient’s response to therapy.

The initial study in this area involved 69 outpatients with heart failure who were randomly assigned to standard care or titration of therapy guided by NT-proBNP levels.\textsuperscript{27} In the active treatment arm of this pilot study, a prespecified algorithm was used to adjust diuretics and ACE inhibitor doses to achieve an NT-proBNP level of less than 1691 pg/mL (200 pm/L). Guided therapy was associated with a significantly lower rate of the composite primary end point of cardiovascular death, hospital admission or symptoms of decompensated heart failure. At 6 months, NT-proBNP–guided therapy was associated with use of modestly higher doses of ACE inhibitors and furosemide.

A cautionary note comes in the form of a cross-sectional analysis involving 558 consecutive outpatients with stable chronic systolic heart failure.\textsuperscript{45} Of the 408 patients in this cohort with incompletely controlled symptoms of heart failure (NYHA class II or III), 106 (21%) had a BNP level of less than 100 pg/mL. In the 60 asymptomatic patients (NYHA class I), the median BNP level was 147 pg/mL and the highest values were over 500 pg/mL. These data suggest that, in addition to BNP levels varying according to age and renal function, BNP levels in heart failure may depend on other currently undefined factors, such as the stage of the disease (early v. late) and genetic polymorphisms present in the patients.\textsuperscript{46} In light of such interindividual variation in BNP levels, use of a common BNP target level to guide therapy may be inappropriate.\textsuperscript{47}

Recently, Jourdain and colleagues reported the initial results of the Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) trial, which randomly assigned 220 outpatients with systolic heart failure (NYHA class II or greater, and ejection fraction < 45%) at a centre in France to either BNP-guided therapy or standard care.\textsuperscript{48} Patients were followed every 3 to 4 months. During a median of 15 months of follow-up, 16% of the BNP-guided group and 27% of the usual-care group either died or were admitted to hospital because of heart failure (p = 0.001). The BNP-Assisted Treatment To Lessen Serial Cardiovascular Readmissions and Death (BATTLE-SCARRED) trial, which has targeted an enrolment of 360 patients, involves 3 arms: usual care, a clinical score–guided therapy arm and an NT-proBNP–guided arm.\textsuperscript{49} Patients are followed every 3 months for a minimum of 1 year. Results are expected in 2007.

Conclusions and future directions

The evidence is strongest that a low BNP level in a patient presenting to the emergency department with acute dyspnea thought possibly to be due to heart failure provides a high level of confidence that heart failure is not responsible for the patient’s symptoms. Evidence on the value of BNP screening for left ventricular dysfunction either in patients with symptoms or in the apparently healthy population is currently less per-
suasive. BNP adds significant prognostic information both for patients with heart failure and for asymptomatic adults, but the appropriate response to this increased risk in either population remains to be defined. Ongoing studies that will report results over the next several years should clarify the value of serial BNP testing in the titration of therapy and will likely have the biggest impact on whether such testing assumes a more central role in the care of patients with heart failure.

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