Sorting Out the Evidence on Natriuretic Peptides

Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA,
Keisha R. Sandberg, MPH

Divisions of Cardiology, Nutrition, and Preventive Medicine, William Beaumont Hospital, Royal Oak, MI

B-type natriuretic peptide (BNP) is a cardiac neurohormone released as pre-proBNP and then enzymatically cleaved to the N-terminal-proBNP (NT-proBNP) and BNP upon ventricular myocyte stretch. Blood measurements of BNP and NT-proBNP have been used to identify patients with heart failure (HF). Clinical considerations for these tests include their half-lives in plasma, dependence on renal function for clearance, interpretation of their units of measure, and the rapid availability of the test results. The BNP assay is currently used as a diagnostic and prognostic aid in HF and as a prognostic marker in acute coronary syndromes (ACS). In general, a BNP level less than 100 pg/mL excludes acutely decompensated HF. In the absence of renal dysfunction, NT-proBNP has also been shown to be of diagnostic value in HF, related to HF severity, predictive of sudden death, and prognostic for death in ACS. This article will sort out the literature concerning the use of these peptides in a variety of clinical scenarios.
[Rev Cardiovasc Med. *2003;4(suppl 4):S13–S19*]

Key words: B-type natriuretic peptide • N-terminal-proBNP • Heart failure • Sudden death • Acute coronary syndromes • Prognosis

With the use of disease-modifying agents, including angiotensin-converting enzyme inhibitors and ß-blockers, the prevalence of heart failure (HF) grew rapidly through the 1990s.[1] In addition, more patients are surviving acute myocardial infarction (AMI) and are left at risk for the development of HF. On average, the 5-year mortality rate for HF is 50%, with 90% of patients

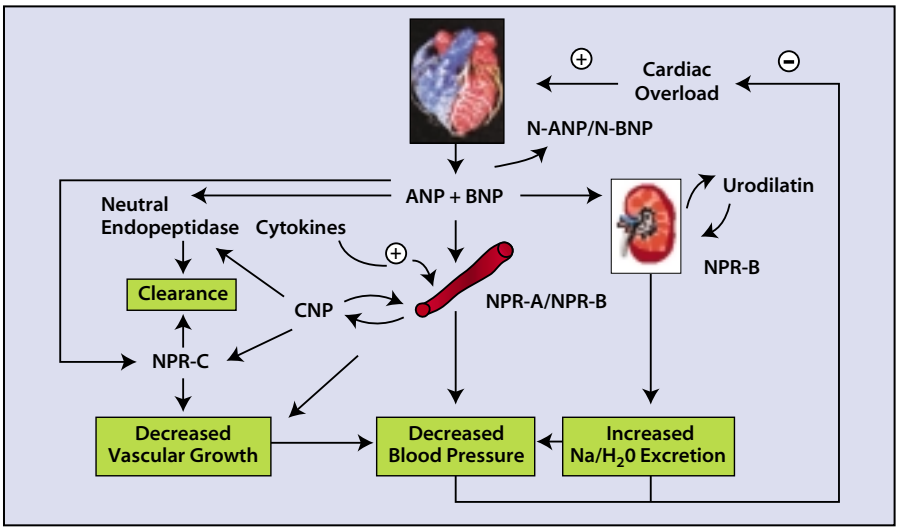

Figure 1. *Stimulation, release, and clearance of natriuretic peptides. N-ANP, N-terminal atrial natriuretic peptide; N-BNP, N-terminal B-type natriuretic peptide; CNP, C-type natriuretic peptide; NPR, natriuretic-peptide receptor. Adapted with permission from Wilkins MR, Redondo J, Brown LA. The natriuretic-peptide family.* Lancet. *1997; 349:1307-1310.*

dead at 10 years.[1] The initial diagnosis of HF remains a clinical challenge.[2] Furthermore, in-hospital mortality and readmission rates for HF patients are high.[1–3] The discovery of B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP) as markers for the diagnosis, severity, and prognosis of HF is truly a breakthrough for clinicians and patients faced with this disorder.

The Natriuretic Peptide Family as Important Cardiac Neurohumoral Markers

The vasodilator natriuretic peptide family could be the best-suited markers for neurohumoral profiling in HF.[4,5] There are three major natriuretic peptides, all sharing a common 17-amino-acid ring structure: atrial natriuretic peptide (ANP), BNP, and C-type natriuretic peptide.[6-8] The synthesis, structure, and function of these peptides are reviewed elsewhere in this supplement. The release and clearance of BNP and NT-proBNP are depicted in Figure 1. BNP levels accurately reflect the decompensated state of circulatory congestion.[9–12] Both BNP and NT-proBNP are independent predictors of high left ventricular end-diastolic pressure and are more useful than ANP or other neurohormones for assessing mortality in patients with chronic HF.[13] The half-life of NT-proBNP is 120 minutes, which suggests that meaningful changes in hemodynamics could be reflected by this test approximately every 12 hours.[14] The half-life of BNP is 22 minutes,[15] and prior studies have established that BNP can accurately reflect pulmonary capillary wedge pressure changes every 2 hours.[16] Hence, the biologic differences in these peptides may leverage specific clinical applications for each.

Comparing BNP and NT-proBNP

Table 1 lists the important differences between BNP and NT-proBNP, the two assays currently approved by the U.S. Food and Drug Administration

Table 1
Distinguishing Features of the Ventricular Natriuretic Peptide Assays

Characteristic	BNP	NT-proBNP
Components	BNP molecule	NT fragment (1–76) NT-proBNP (1–108)
Molecular weight	3.5 kd	8.5 kd
Hormonally active?	Yes	No, inactive peptide
Genesis	Cleavage from NT-proBNP	Release from ventricular myocytes
Half-life	22 min	120 min
Clearance mechanism	Neutral endopeptidase clearance receptors	Renal clearance
Increases with normal aging	+	++++
Correlation with estimated glomerular filtration rate	−0.20	−0.60
Approved cutoff(s) for HF diagnosis	100 pg/mL	Age < 75 y: 125 pg/mL Age ≥ 75 y: 450 pg/mL
Available at the point of care?	Yes	No
Studies completed	1370	39
Entry on U.S. market	November 2000	December 2002

BNP, B-type natriuretic peptide; NT-proBNP, N-terminal-proBNP; HF, heart failure.

(FDA) for use in North America. The strengths of the BNP assay are that 1) it is available at the point of care for rapid diagnosis; 2) it is less influenced by age and renal function; and 3) it has a single, approved cut-point for the diagnosis of HF that has been validated in multiple clinical settings.[15-16] BNP is U.S. FDA-approved as a diagnostic aid in HF and as a prognostic indicator in acute coronary syndromes (ACS).[15] As of 2003, BNP should be considered the gold standard natriuretic peptide for clinical application. The strengths of NT-proBNP include its use on large laboratory platforms for economies of scale.[14] The strong correlation between NT-proBNP levels and renal function has led some investigators to suggest that NT-proBNP might be an overall marker of cardiorenal function. Importantly, the diagnostic cutoff for NT-proBNP depends on the patient's age. Because the normal decline in glomerular filtration rate that occurs with age influences NT-proBNP, the cutoff for detecting HF jumps from 125 to 450 pg/mL after age 75 years.[14] For the peak age incidence of HF (65–85 years), there is a considerable "grey zone" for NT-proBNP, in which the test has little value or is potentially confusing to clinicians. Importantly, neither BNP nor NT-proBNP are cleared with hemodialysis.[17] In patients with end-stage renal disease, BNP is usually elevated before dialysis and drops 15%–30% over a 3-hour dialysis period.[18] Levels of NT-proBNP, however, remain elevated before and after dialysis, and hence cannot be used to guide volume status in this population.[18]

Putting BNP and NT-proBNP into Practice

Evaluating dyspnea can be a challenge. In the urgent care setting, it is often difficult to distinguish between cardiac and pulmonary causes of dyspnea.[2] A misdiagnosis could place the patient at risk for both morbidity and mortality, especially if treatment is inappropriate. Pulmonary diseases, including asthma and emphysema, are common in the elderly and often overlap or are confused with one another.[19,20] In approximately 20% of patients labeled with "asthma" or "emphysema" in the emergency department (ED), BNP levels will be elevated, and the patients will ultimately be correctly diagnosed with HF.[20] Thus, BNP offers a considerable opportunity for obtaining the correct diagnosis in a dyspneic patient and initiating appropriate therapy.

Ventricular stiffening is more pronounced in women and in the elderly, hence in all populations women and older individuals have slightly higher BNP and NT-proBNP levels than do men.[21] For both men and women, over the course of a lifetime, BNP levels should gradually rise but in general remain lower than 50 pg/mL, unless there is the development of left ventricular systolic or diastolic dysfunction (Figure 2). There is no difference in BNP levels between Caucasian and African American patients.[22] There have been insufficient studies with NT-proBNP to determine racial differences at this time. There are no significant differences in BNP levels between normal patients with hypertension or diabetes and age-matched control subjects.[23,24] As discussed above, both BNP and NT-proBNP can be elevated in the setting of chronic kidney disease because of volume overload.[17,25] However, BNP is thought to be the superior test in diagnosing HF in

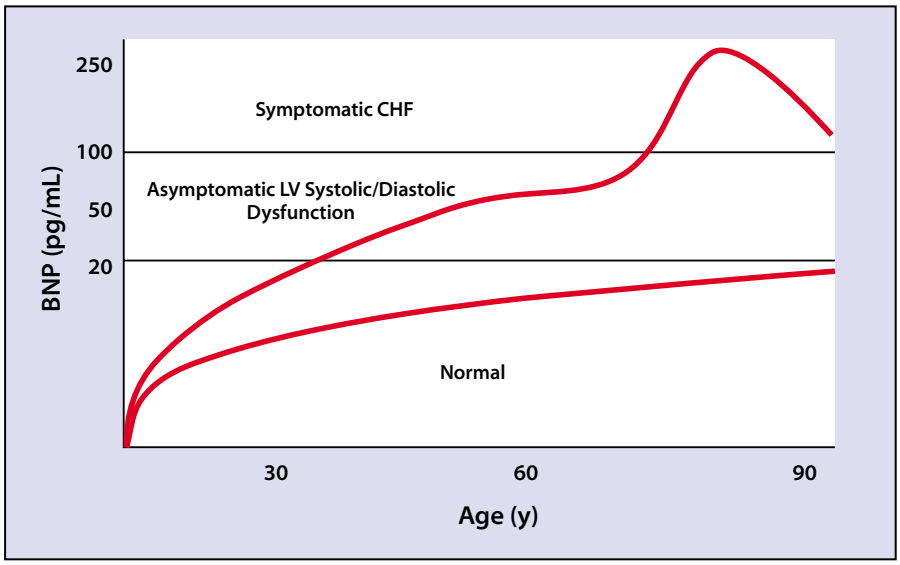

Figure 2. *Natural rise of B-type natriuretic peptide (BNP) with age over the course of a lifetime. CHF, congestive heart failure; LV, left ventricular.*

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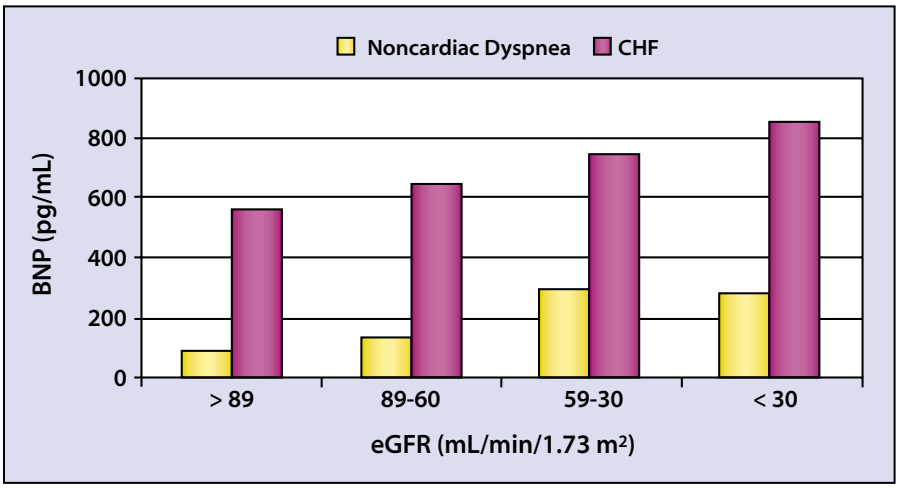


Figure 3. *Levels of B-type natriuretic peptide (BNP) according to renal function in terms of estimated glomerular filtration rate (eGFR) in those with and without congestive heart failure (CHF). Reproduced with permission from McCullough et al.*[25]

patients with elevations in serum creatinine, given the wide separation (more than 500 pg/mL) between those with and without HF (Figure 3).[25] Hence, B-type natriuretic peptides must be viewed in conjunction with the clinical scenario and patient characteristics, including age, gender, and presence or absence of renal disease.

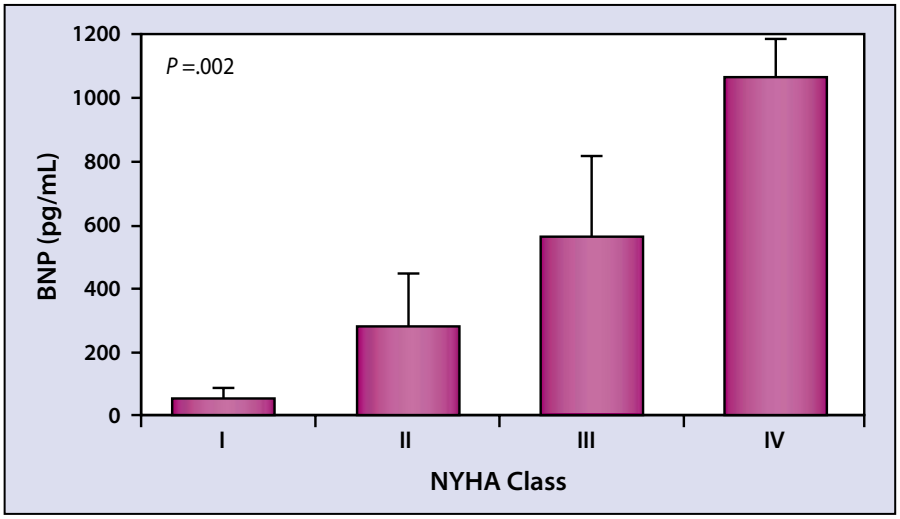
BNP and NT-proBNP and Heart Failure Severity

The New York Heart Association (NYHA) functional system of classification correlates well with symptoms and mortality in patients with HF, but it is a subjective system that depends on patient self-report and physician assignment. Both BNP and NT-proBNP have been shown to accurately reflect heart failure severity; hence, these blood tests have inherent, objective contributions to make to patient assessment.[26] Because BNP levels correlate to elevated end-diastolic pressure and left ventricular wall tension, and because end-diastolic pressure is linked closely with dyspnea, it follows that BNP levels correlate well with HF functional class (Figure 4). Levels of NT-proBNP lag behind the clinical picture, given its longer time for clearance from the blood pool, and hence may not represent the clinical state at the time the patient is examined. Importantly, when BNP and NT-proBNP have been compared in head-to-head studies, BNP has been found to be slightly more accurate in identifying those patients with reduced left ventricular systolic function (Figure 5).[27]

Use in Emergency and Critical Care

Point-of-care testing allows diagnostic assays to be performed in locations such as the ED or intensive care unit, so that treatment based on the results can be administered immediately. In the Breathing Not Properly Multinational Study, BNP levels were measured upon arrival in 1586 patients who presented with acute dyspnea, and the ED physicians (blinded to BNP levels) were asked to assess the probability of the patient having HF.[28,29] Two independent cardiologists, also blind to the BNP levels, later reviewed all clinical data and standardized scores to produce a "gold standard" clinical diagnosis. A BNP cutoff value of 100 pg/mL had a sensitivity of 90% and a specificity of 76% for differentiating HF from other causes of dyspnea. A cutoff level of 50 pg/mL had a negative predictive value of 96%.[30] Very importantly, a single, point-of-care test of BNP level performed immediately upon arrival to the ED had more diagnostic accuracy than did the clinician with all the tools available, including history, physical

Figure 4. *Relationship between B-type natriuretic peptide (BNP) with New York Heart Association (NYHA) functional classification. Reproduced with permission from Kuster GM, Tanner H, Printzen G, et al. B-type natriuretic peptide for diagnosis and treatment of congestive heart failure.* Swiss Med Wkly. *2003;133:623-628.*



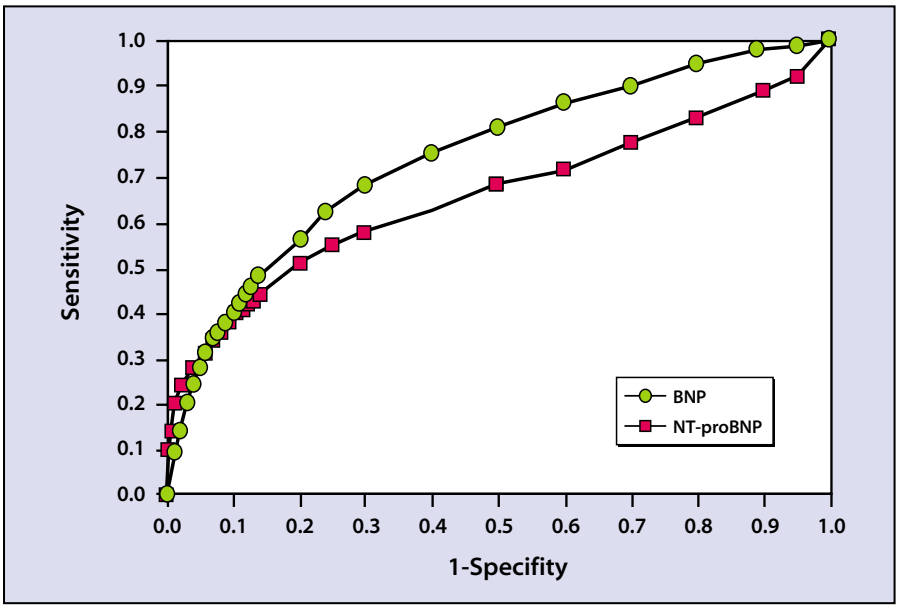


Figure 5. *A comparison of area under the receiver operating characteristic curve (AUC) for B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP) in the diagnosis of reduced left ventricular ejection fraction (LVEF). For the detection of resting LVEF < 40%, BNP was numerically the best marker, with an AUC of 0.83 ± 0.06, compared with NT-proBNP with a slightly smaller AUC of 0.79 ± 0.07,* P = ns. *Reproduced with permission from Hammerer-Lercher et al.*[27]

examination, conventional laboratories, chest x-rays, and review of old records.[29]

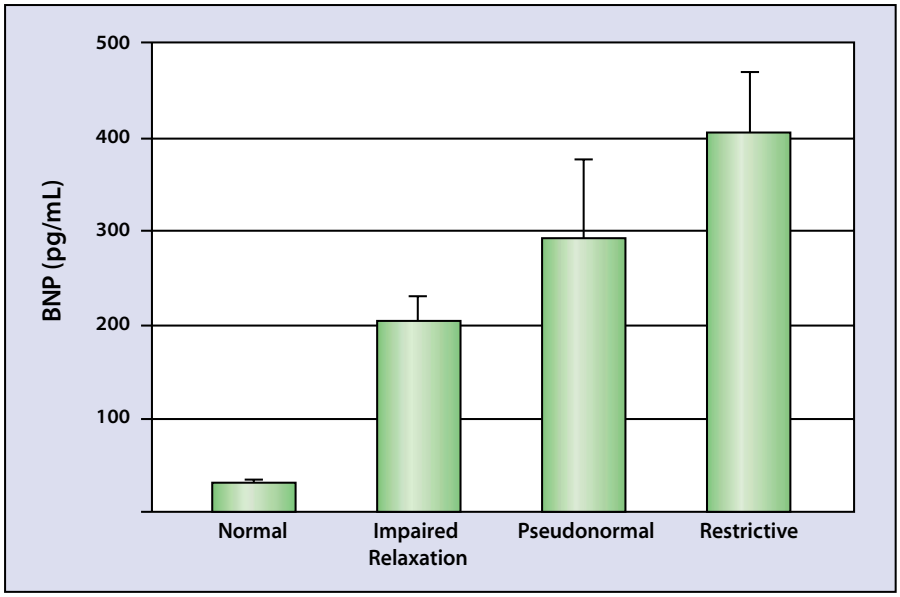
Importantly, BNP is useful in establishing the diagnosis of diastolic HF, which up until recently has been a very difficult diagnosis to make.[26,30] Although levels tend to be lower for diastolic compared with systolic HF, they are sufficiently elevated to detect HF.[30] In addition, the elevation in BNP parallels the severity of diastolic dysfunction according to the Doppler filling patterns seen on mitral inflow and pulmonary venous flow.[26] Figure 6 shows the incremental rise in BNP expected as the echocardiographic grading of diastolic dysfunction becomes more severe. There have been no studies of NT-proBNP in the detection of diastolic HF.

B-type natriuretic peptide has proven usefulness in hospitalized patients with both systolic and diastolic HF. A study of hospitalized patients (n = 72) admitted with decompensated NYHA class III–IV HF recorded daily BNP levels.[31] In 22 patients, BNP levels increased during hospitalization (mean increase 232 pg/mL; $P < .001$); these patients ultimately died or were readmitted. In the remaining patients, BNP decreased during treatment (mean decrease 216 pg/mL), and these patients had favorable outcomes. In general, it is prudent to measure BNP or NT-proBNP as soon as possible after arrival to the ED and on the day of planned discharge home.[31] Failure of these levels to drop over time, or an absolute BNP level > 500 pg/mL, predicts readmission and death. In such patients, a careful review of medications and intensification of therapy, if possible, is indicated.

Markers for Future Sudden Death

A study of 452 ambulatory patients with a left ventricular ejection fraction (LVEF) < 35% found that, in patients with mild to moderate HF (NYHA class I–II), BNP levels were independent predictors of sudden death.[32] A cutoff BNP level of 130 pg/mL differentiated patients with high and low survival rates from those with sudden death. Only 1%

Figure 6. *B-type natriuretic peptide (BNP) levels in patients with diastolic dysfunction by echocardiography. Adapted from Maisel et al.*[28]



(1 of 110) of those patients with BNP levels less than the cutoff point died suddenly, compared with a sudden death rate of 19% (43 of 227) among those patients with BNP levels greater than the cutoff point. In this study, when BNP and NT-proBNP were considered together as prognostic markers, only BNP was found to independently predict sudden death.[32] Other studies support the notion that BNP can help predict death, especially in the elderly with HF.[33]

In 2525 ACS patients, elevated BNP values predicted worsened survival and HF hospitalizations across the entire spectrum of acute coronary syndromes.

Identifying High-Risk Acute Coronary Syndrome Patients

The relation between NT-proBNP levels and prognosis after AMI was reported by Richards and colleagues.[34] Both BNP and NT-proBNP obtained in the subacute phase were predictive of long-term, all-cause mortality, as well as readmissions for HF after AMI.[34] Two studies have suggested that circulating BNP and NT-proBNP but not ANP levels are higher in patients with unstable angina than in patients with stable coronary artery disease.[35,36] The prognostic value of NT-proBNP in patients with unstable angina or non-ST segment elevation myocardial infarction (NSTEMI) has also been demonstrated. Circulating NT-proBNP levels were significantly associated with death within 43 days and provided complementary prognostic information to conventional risk markers, including troponin I.[36] In 2525 ACS patients, including subgroups with unstable angina and NSTEMI, elevated BNP values predicted worsened survival and HF hospitalizations across the entire spectrum of ACS.[37] Moreover, the study demonstrated for the first time that BNP was predictive of recurrent ischemic events when the level was greater than 80 pg/mL.

The prognostic value of NT-proBNP across the spectrum of ACS has also been evaluated in a large cohort of patients.[38] NT-proBNP levels were strongly related to long-term mortality in patients with all forms of ACS. Importantly, the relationship remained significant after adjustment for conventional risk markers, including LVEF. Of interest, NT-proBNP was prognostic in the subgroup of patients with no signs of HF (Killip class I) during the index hospitalization. These studies suggest that the B-type natriuretic peptides are akin to an early window for the Killip classification, in that they identify patients with large infarctions and impending left ventricular dysfunction.

Conclusions

The measurement of natriuretic peptides for the diagnosis of HF has been a major breakthrough in cardiology. Both BNP and NT-proBNP assays are available to clinicians. There are important differences between these tests, especially with respect to the influence of age and renal function, which give an edge to BNP as the diagnostic test of choice. Taken in aggregate, the considerable knowledge base for BNP (and to a lesser extent for NT-proBNP) provides evidence that these peptides are important components of HF diagnosis and management. ■

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Main Points

- In a patient presenting with dyspnea, heart failure (HF) is usually absent at B-type natriuretic peptide (BNP) levels less than 100 pg/mL, possible between 100–500 pg/mL, and probable at levels greater than 500 pg/mL. BNP levels between 100 and 500 pg/mL might also be seen in patients with known left ventricular dysfunction, lung disease (BNP produced from the right ventricle), renal failure, myocardial infarction, or pulmonary embolism.
- N-terminal-proBNP (NT-proBNP) levels greater than 125 pg/mL in those younger than 75 years and greater than 450 pg/mL in those older than 75 reflect the presence of HF. Because NT-proBNP is influenced considerably by age and its related normal decline in glomerular filtration rate, these two cutpoints must be used. NT-proBNP levels between 125 and 450 pg/mL in the elderly should be considered nondiagnostic until more data are available.
- In patients hospitalized with HF, failure of the BNP to drop over the hospitalization or a discharge BNP level greater than 500 pg/mL predicts high rates of readmission and death.
- In acute coronary syndromes, elevations in BNP or NT-proBNP predict higher rates of recurrent ischemic events, readmission for HF, and death, even in Killip class I patients.

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